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# FATTY INFILTRATION IN THE LIVER — RESPONSE TO TREATMENT

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INFILTRATION of fat in the liver may be produced experimentally in animals by dietary restriction of proteins, choline and precursors of choline, vitamin-B complex, as well as by the administration of hepatotoxins. Von Mering and Minkowski,[1] in studying diabetes, reported in 1890 the frequent occurrence of fatty liver in depancreatized dogs. In 1924, Allan, Bowie, Macleod, and Robinson,[2] and Fisher[3] noted that large fatty livers developed in depancreatized dogs maintained on insulin for long periods. These findings led one of us (C.H.B.[4]) to suggest that liver function studies should be conducted on all diabetic patients.

In 1932, Best, Hershey, and Huntsman[5] by dietary means produced fatty infiltration in the livers of normal rats in about three weeks, while six months was required for similar changes to appear in the depancreatized dog. Chaikoff and associates[6,7] produced definite cirrhotic changes both in pancreatectomized and in normal dogs by prolonged feedings of diets that stimulated the accumulation of fat in the liver. Subsequently, several other investigators reported similar lesions occurring in rats on deficient diets.

Best, Hartroft, and Sellers[8] reported that in experimental animals on a low-choline diet, stainable lipids first appeared in the liver as small intracellular globules. Subsequently the globules coalesced to form large spherical masses distending the cell membrane. The membranes of the liver cells, distended with fat, were increasingly stretched until the cell membranes broke and fatty cysts were formed in from six to nine weeks. With the rupture of the fatty cysts,

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definite cirrhotic changes occurred with fibrosis and increase in connective tissue.

Allan and associates[2] reported that the fatty infiltration of the liver in depancreatized dogs was prevented by the oral administration of raw beef pancreas. Hershey,[9] and Hershey and Soskin[10] reported that crude egg lecithin produced the same protective effect as that of raw beef pancreas. Best and associates[5,8] identified choline as the active principle in lecithin. They reported that, within limits, after using a diet deficient in protein or choline for approximately six weeks, the administration of choline reversed the fatty infiltration and prevented the development of fibrosis. After the fatty cysts had ruptured, the subsequent administration of choline did not prevent the development of fibrosis or cirrhotic changes.

The lipotropic effect of these substances has been thought to result from an increase in the formation and turnover of phospholipids.[11] In the experimental animal, Artom and Cornatzer, [12] and Perlman, Stillman, and Chaikoff[13] by using radioactive phosphorus have shown that choline and methionine will increase the phospholipid turnover in the liver.

Laennec's cirrhosis in man has been thought by many to result from the same mechanism as that which produces cirrhosis in the experimenttal animal; this concept has not been proved.[14] While dense fatty infiltration of the liver frequently occurs in man, the large fatty cysts as seen in the experimental animal have not been observed.

Not one, but various types of fatty infiltration of the liver may occur in man, and each type may respond to a therapy designed to correct the specific etiologic agent. Fatty liver may be classified[8] on the basis of four general causes: (1) dietary deficiencies (specifically proteins, choline, and vitamin-B complex); (2) hormonal imbalance (insulin deficiency); (3) lack of oxygen (anemia or ischemia of liver cells); and (4) toxic or infectious processes that damage the liver cell.

Extensive fatty infiltration of the liver can cause enlargement of the liver, ascites, edema, jaundice, and all of the clinical and laboratory findings of hepatic failure. Clinically, the response of the patient with fatty infiltration of the liver is much better than that of the patient with severe fibrosis. In a patient in hepatic failure we prefer to see only fatty infiltration on the needle biopsy[15,16] since there is a much more favorable prognosis than if considerable fibrosis is present. As in the experimental animal, in man the fatty liver with no fibrosis can be restored to normal function and architecture by adequate treatment. In contrast, there is little we can do to remove the scarring or fibrosis that has already occurred.

## Report of Cases

The following case histories are presented to demonstrate: (1) the great severity of hepatic failure that can be associated with extensive fatty infiltration of the liver; (2) the diminution in fat in the liver after intensive medical therapy,

as shown by serial specimens of needle biopsies of the liver; (3) the improvement in the clinical picture and in the results of liver function studies after medical treatment.

**Case 1.** A 48-year-old woman was first admitted to the Cleveland Clinic Hospital on February 27, 1959, because of jaundice, progressive abdominal distention, and loss in weight of four weeks' duration. She previously had had prolonged treatment for chronic alcoholism in three other hospitals, and also had been hospitalized for "liver disease" and ascites in 1952; paracentesis had been performed several times and 3,700 ml., 10,800 ml., 300 ml., and 4,500 ml., respectively, of ascitic fluid had been removed.

Physical examination revealed a poorly nourished, emaciated, chronically ill patient who was 62 inches tall and weighed 113 pounds. The skin was jaundiced and palmar erythema was present. The abdomen was distended with fluid, a fluid wave being present; the liver was enlarged 8 cm. below the costal margin, and the spleen was palpable.

Laboratory examinations showed the blood count, blood sugar, blood urea, Wassermann test results, serum electrolytes, stool, and urinalysis to be normal or negative. Liver function studies *(Table 1)* showed the presence of moderate jaundice, a

**Table 1.**—*Results of liver function tests in case 1*

| Test | 1959 | | | |
|---|---|---|---|---|
| | February | April | May | July |
| Bilirubin, mg./100 ml. | | | | |
| Direct | 18.8, 15.1 | 2.2, 3.6 | 0.6 | 0.5 |
| Indirect | 20.0, 11.1 | 1.1, 2.4 | 1.4 | 0.2 |
| Albumin, gm./100 ml. | 2.3, 3.10 | 3.29 | 3.3 | 4.40 |
| Globulin, gm./100 ml. | 2.7, 2.40 | 2.29 | 3.5 | 2.70 |
| Prothrombin time, percentage of normal control | 68% | 86% | 80% | 100% |
| Serum transaminase, S. G. O. units | 160 | 115, 35 | — | 20 |
| Thymol, units | 7 | 3 | 3 | 4 |
| Cephalin, units | 2+ | 1+ | 0 | 0 |

reversal of the albumin-globulin ratio, and indications of active liver disease with an elevation of the transaminase and a 2 plus cephalin-cholesterol flocculation test. The electrocardiogram was normal. Roentgenograms revealed a normal chest and colon, but examination of the esophagus suggested small varices throughout.

Treatment consisted of a 3,000-calorie diet, high in proteins and carbohydrates, but low in salt and fat; choline dihydrogen citrate, 20 gr., three times daily; vitamin-B

complex twice daily; Decadron,* 0.75 gr. twice daily, and neomycin, 0.5 gm. four times daily. She also received parenteral injections of vitamin K, vitamin $B_{12}$ every other day, mercuhydrin daily, and depotestosterone twice weekly. Because of her extreme nervousness, she was give a course of prochlorperazine, 10 mg. four times daily. A few days later, a Parkinson-like syndrome† with tremor of the hands developed, which disappeared when administration of prochlorperazine was discontinued and Artane‡ and Cogentin§ were given. After five weeks she was discharged (April 7, 1959) and was advised to continue with the same therapy. Significant improvement was observed in the results of liver function studies and in the jaundice, and a notable diminution in the extent of fatty changes in the liver as demonstrated by repeated needle biopsies *(Fig. 1)*.

Six weeks later (in May) when she underwent progress studies she appeared improved. She had abstained from alcohol and had followed the program she received in the hospital. Her appetite had increased and she had gained 13 pounds. There no longer was any evidence of ascites or jaundice, and the liver was not palpable.

Repeated liver function tests substantiated her clinical improvement *(Table 1)*. Changes in therapy at that time included discontinuance of Decadron and mercuhydrin, a reduction in the number of vitamin-$B_{12}$ injections to one each week, and the giving of vitamin K orally rather than parenterally. The choline dosage was reduced to 10 gr. three times daily. When last examined as an outpatient on July 24, 1959, her general condition was still improving. She had a good appetite and had gained 29 pounds in six months; she had abstained from alcohol; there was no evidence of jaundice, hepatomegaly, or ascites.

**Case 2.** A 65-year-old railroad conductor was admitted to the Cleveland Clinic Hospital on April 15, 1959, because of an episode of hematemesis involving about a half cupful of bright-red blood. He had not had any tarry stools, but for several weeks he had occasional nausea and vomiting of clear fluid. He was a chronic alcoholic throughout adulthood, and for the last few months had missed many days of work because of increased alcoholic intake. He had a history of duodenal ulcer with massive hemorrhage in 1939, but had no symptoms of ulcer since then. In July, 1950, he was operated on for papillary transitional carcinoma of the bladder; cystectomy and bilateral ureterosigmoidostomy were performed.

Physical examination revealed an elderly plethoric man who weighed 150 pounds; he was nervous, agitated, and had a coarse tremor of the head, shoulders, and hands. The skin was not jaundiced; palmar erythema was present. The liver was soft, nonnodular, and was enlarged 6 cm. under the right costal margin.

The significant laboratory findings were as follows: the blood hemoglobin content was 16.5 gm. per 100 ml., white-cell count 5,200 per cu. mm., and a normal differential count. Two consecutive stool examinations for occult blood were negative. Blood urea was 24 mg. per 100 ml. The urinalysis, blood sugar, electrolytes and results of the

**Decadron (dexamethasone), Merck Sharp & Dohme.*

*†We have seen a Parkinson-like syndrome in four other patients with severe liver disease; two of these patients had undergone portacaval shunt procedures. In each instance, the Parkinson-like syndrome was aggravated by prochlorperazine.*

*‡Artane (trihexyphenidyl), Lederle Laboratories.*

*§Cogentin {methanesulfonate (benztropine methanesulfonate, Merck)}, Merck Sharp & Dohme.*

Wassermann test, were either normal or negative. The liver function studies showed high retention of Bromsulphalein *(Table 2)*.

**Table 2.**—*Results of liver function tests in case 2*

| Test | 1959 | |
|---|---|---|
| | April | July |
| Bilirubin, mg./100 ml. | | |
| Direct | 0.2 | 0.2 |
| Indirect | 0.8 | 0.2 |
| Albumin, gm./100 ml. | 4.16 | 3.67 |
| Globulin, gm./100 ml. | 2.49 | 2.78 |
| Prothrombin time, percentage of normal in 14 sec. | 100% | 100% |
| Cephalin, units | 0 | 0 |
| Bromsulphalein, percentage of retention in 45 minutes | 21% | 3% |
| Alkaline phosphatase, units | 2.9 | — |

Roentgenograms of the esophagus, stomach, and duodenum showed no abnormality. Esophagoscopy, performed a few days later, showed no evidence of erosion, ulceration, or varices throughout the entire length of the esophagus. An intravenous urogram showed evidence of bilateral caliectasis, and a roentgenogram of the chest was normal.

The patient was given the following regimen: rest; a 3,000-calorie diet, high in proteins and carbohydrates; vitamin-B complex, three times daily; supplemental protein feeding, two and one-half hours after meals; an anticholinergic agent, four times daily; an antacid, four times daily; and sedation. The cause of the hematemesis remained undetermined and was thought to have been associated with the strain of retching and not due to ulcers or varices. He was discharged from the hospital and advised to follow the above-outlined program. On July 1, 1959, he was readmitted for progress studies. At that time the patient was feeling well; he had gained ten pounds in weight. He had had no hematemesis or tarry black stools since April. The liver was not palpable.

The Bromsulphalein retention tests showed improvement in liver function *(Table 2)*, and a specimen of a needle biopsy of the liver showed a significant decrease in fatty infiltration *(Fig. 2)*.

**Case 3.** A 50-year-old woman was admitted to the Cleveland Clinic Hospital on February 2, 1959, because of epigastric pain (relieved by alkali and food) loss of 25 pounds in weight, and severe generalized malaise of one year's duration. These symptoms were dated from a cholecystectomy, which was performed in 1958 at another hospital. She customarily consumed a half pint to one pint of whisky a day for many years.

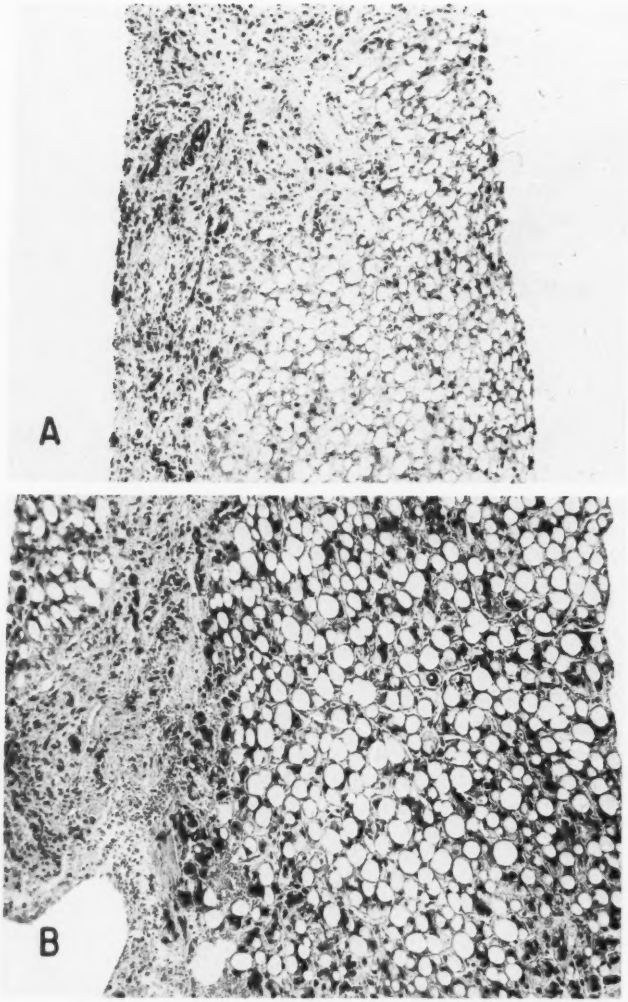
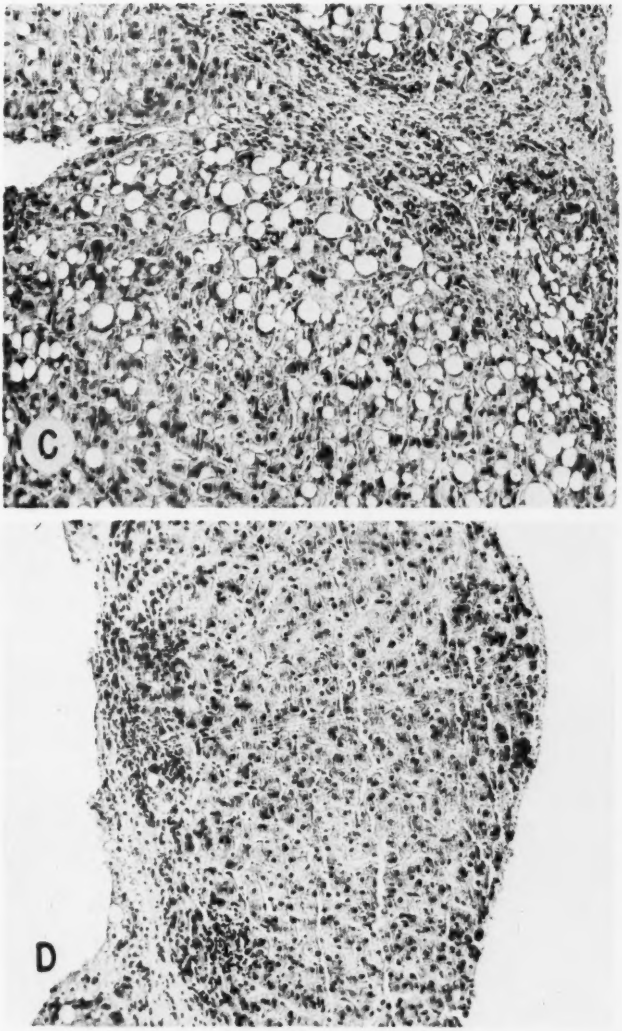



**Fig. 1.** Case 1. A, Needle biopsy specimen on March 3, 1959. Section shows extensive fatty replacement with only sparse parenchymal cells scattered between the fat globules. Some fibrosis is seen in the periportal areas (on the left side); magnification x 100. B, Needle biopsy specimen on March 17, 1959, again shows an extensive infiltration of fat in the hepatic parenchyma. Some bile stasis is present within the hepatic nodules, which are separated by moderately broad fibrotic portal zones containing proliferating bile ducts and a minimal amount of chronic inflammatory infiltrate; magnification x 100. C, Needle biopsy specimen on April 2, 1959, revealing a decrease in the fatty




change and in the bile stasis in comparison with the two previous specimens. Periportal fibrosis is present, but some normal liver cells without fat globules, which are difficult to find on the previous specimens, are present; magnification x 100. D, Needle biopsy specimen on May 11, 1959, reveals almost complete disappearance of fat. The hepatic parenchymal cells, which were hardly visible in the first biopsy specimen, now show no significant abnormality. The normal lobular architecture is still distorted by bands of connective tissue and fibrosis; magnification x 100.

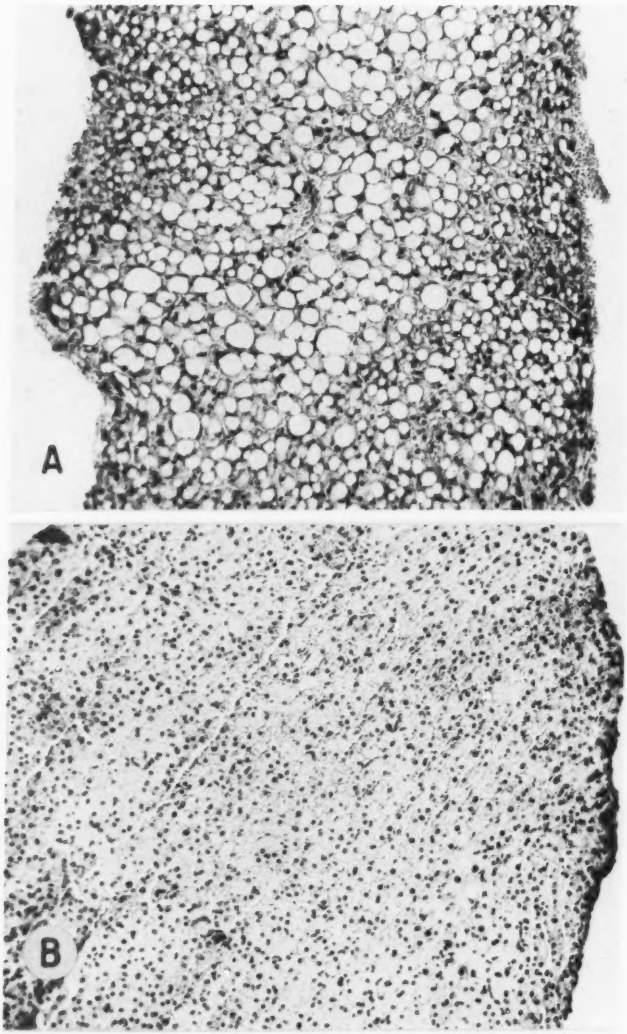



**Fig. 2.** Case 2. A, Needle biopsy specimen on April 17, 1959, showing an extensive fatty replacement throughout the entire specimen; magnification x 100. B, Biopsy specimen on July 1, 1959. showing a marked decrease in the fatty infiltration; the liver cells appear well-glycogenated with only an occasional cell showing fat in the cytoplasm. In contrast to case 1, there does not appear to be an increase in fibrous tissue; magnification x 100.

The physical examination revealed a pale and emaciated woman who was 62 inches tall and weighed 99 pounds. Palmar erythema and icterus of the sclerae were present. The abdomen was distended; a fluid wave was found. The liver was enlarged, extending 10 cm. below the right costal margin, with a sharp edge, and was tender to palpation. The spleen was palpable.

The significant laboratory findings were as follows: blood hemoglobin concentration, 11.4 gm. per 100 ml.; and a white-cell count, 5,100 per cu. mm. with a normal differential count. A guaiac test of the stool was positive. The blood sugar, blood urea, urinalysis, serum electrolytes, and Wassermann test results were either normal or negative. The liver function studies showed impaired function *(Table 3)*.

**Table 3.**—*Results of liver function tests in case 3*

| Test | 1959 | | |
|---|---|---|---|
| | February | April | August |
| Bilirubin, mg./100 ml. | | | |
| Direct | 0.7 | 0.5 | 0.2 |
| Indirect | 1.2 | 0.7 | 0.2 |
| Albumin, gm./100 ml. | 3.0 | 3.3 | 4.5 |
| Globulin, gm./100 ml. | 2.5 | 3.5 | 2.7 |
| Prothrombin time, percentage of normal control | 62% (19 sec.) | 100% (14 sec.) | 100% (14 sec.) |
| Thymol, units | 6 | 7 | 4 |
| Cephalin, units | 2+ | 1+ | 0 |
| Bromsulphalein, percentage of retention in 45 minutes | 19% | | |
| Alkaline phosphatase, units | 6.4 | — | 3.5 |

Treatment in the hospital consisted of: a smooth diet high in proteins and carbohydrates, and low in salt; a lipotropic agent three times daily, multivitamins twice daily; prochlorperazine, 10 mg., three times daily; and intramuscular injections of vitamin K, once a day. The patient also received an intramuscular injection of vitamin $B_{12}$, 1,000 μg., twice weekly. The course in the hospital was uneventful. She was discharged on February 20 and was asked to continue the same therapy with strict avoidance of alcohol.

She was re-examined in April, 1959. At that time she was feeling much better, her appetite had increased, and she had gained 14 pounds in weight. The liver was still palpable, 4 cm. below the right costal margin, but there was no evidence of ascites. In the meanwhile, a Parkinson-like syndrome developed, which promptly disappeared when administration of prochlorperazine was discontinued and Artane with a meprobamate was given (see footnote to case 1).

On August 5, 1959, she was admitted to the hospital because of an accidental fracture of the eighth dorsal vertebra two months previously. At this time, the results of liver function tests showed a remarkable improvement *(Table 3)*. Progress needle biopsy specimens of the liver substantiated the clinical and laboratory improvement in the liver function *(Fig. 3)*. She was discharged on August 12 and was advised to follow this program: a high-protein, low-salt diet; vitamin-B complex, once a day; vitamin-$B_{12}$ injections once a week; chlorothiazide, 0.5 gm. three times a week; meprobamate, 400 mg. four times daily.

**Case 4.** A 40-year-old physician was examined at the Cleveland Clinic Hospital on August 17, 1948, because of dizzy spells and mental fatigue of six weeks' duration. He had been a heavy drinker most of his adulthood, consuming from one to three quarts of whisky daily.

The physical examination revealed an obese patient who weighed 250 pounds. The skin was jaundiced. The liver was smooth, soft, and enlarged, extending 12 cm. below the right costal margin. The results of laboratory examinations were as follows: the blood hemoglobin content, 12.0 gm. per 100 ml.; a white-cell count, 6,350, and a normal differential count. The urinalysis, blood sugar, serum electrolytes, and Wassermann test results were either normal or negative. The results of the liver function studies are presented in *Table 4*. Roentgen examination of the gastrointestinal tract revealed a duodenal diverticulum and multiple diverticula in the hepatic flexure and the sigmoid colon.

**Table 4.**—*Results of liver function tests in case 4*

| Test | Aug., 1948 | June, 1949 | Nov., 1949 | Jan., 1950 | July, 1950 | July, 1951 | Jan., 1952 | July, 1953 | April, 1956 |
|---|---|---|---|---|---|---|---|---|---|
| Bilirubin, mg./100 ml. | 0.8 (Total) | 2.5 (Total) | 0.8 (Total) | 2.5 (Total) | — | 0.4 (Direct) 0.5 (Indirect) | — | 0.3 (Direct) 0.5 (Indirect) | 0.3 (Direct) 0.5 (Indirect) |
| Albumin, gm./100 ml. | 4.8 | — | — | 5.2 | — | 4.9 | 5.4 | 4.9 | — |
| Globulin, gm./100 ml. | 4.3 | — | — | 4.4 | — | 3.3 | 3.6 | 3.3 | — |
| Prothrombin time, percentage of normal control | — | — | 100% | 100% | — | 100% | 100% | — | — |
| Thymol, units | 1.6 | — | — | 1.0 | — | — | — | — | — |
| Cephalin, units | — | — | 0 | — | — | 0 | — | 0 | — |
| Bromsulphalein, percentage of retention in 45 minutes | 32% | 24% | 28% | 12% | 18% | 15% | 20% | 15% | 7% |
| Alkaline phosphatase, units | 4.6 | — | — | — | — | — | — | — | — |

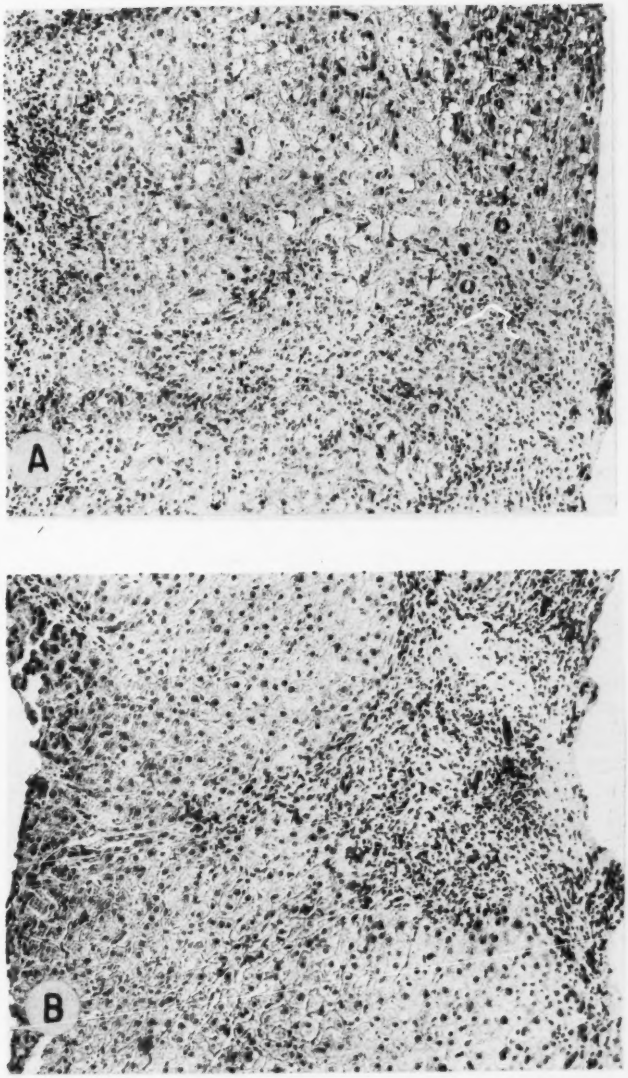



**Fig. 3.** Case 3. A, Needle biopsy specimen on February 6, 1959, revealing distortion of the normal hepatic architecture by broad zones of fibrous and collagenous tissue. The liver cells contain a moderate amount of fat globules; magnification x 100. B, Biopsy specimen on August 6, 1959, shows no change in the fibrosis, but the infiltration of fat has disappeared; magnification x 100.

Treatment in the hospital consisted of a diet that was high in proteins and carbohydrates and low in fat; choline dihydrogen citrate, 10 gr. three times daily; multivitamins, twice a day; and injections of liver extract twice weekly. Upon discharge on August 27 he was advised to follow the same program, and to return for examinations at intervals. Despite the advice to stop drinking, he drank sporadically but followed the rest of the program. The liver gradually decreased in size. It was two fingerbreadths below the right costal margin in March, 1949, one fingerbreadth in June, 1949, and was not palpable in November of the same year.

Because of intermittent episodes of severe pain in the right upper quadrant, along with the nausea and vomiting, the patient was admitted to the hospital on January 1, 1950. Roentgen examination showed a nonfuctioning gallbladder, and a cholecystectomy was performed on January 26. The gallbladder was found to be diffusely inflamed. A biopsy specimen of the liver was obtained *(Fig. 4)*.

Postoperatively the patient again began to drink heavily, consuming about two quarts of whisky daily. Despite the alcoholic intake, he followed the diet and continued daily to take choline and multivitamins, and weekly injections of liver extract. At the last examination in April, 1956, the patient had abstained almost entirely from alcohol; the liver was not palpable, and the Bromosulphalein test showed a 7 per cent retention of the dye after 45 minutes.

## Treatment of the Patient with Fatty Infiltration of the Liver

The basic treatment for fatty infiltration of the liver was the same for each of the four patients. It should be noted that each of the patients was an alcoholic and each had a nutritional or Laennec's type of cirrhosis (in contrast to postnecrotic cirrhosis). The first three patients cited, abstained completely from alcohol. The fourth patient reduced his alcoholic consumption and followed the rest of his "liver program." Although alcohol itself may not cause the hepatic changes described, we believe that it is essential that patients with liver disease, particularly with Laennec's or nutritional cirrhosis or with fatty infiltration avoid the use of alcohol.

A high-protein, high-calorie intake is as essential to the treatment of liver disease as is the avoidance of alcohol. The actual fat content of the diet is of least importance and is adjusted to keep the diet palatable; vitamin-B complex orally and vitamin B and crude liver extract parenterally, are used primarily to increase the appetite. In addition, supplemental protein feedings, such as one of the protein powders or eggnogs, are given two hours after meals. Lipotropic substances such as choline are given as a supplement to insure that adequate amounts are available to mobilize the fat from the liver.

Other therapy, such as vitamin K, testosterone and other hormones for the effect on nitrogen metabolism, steroids, and tranquilizers, is given depending upon the individual needs of the patient. Salt restriction is imposed and diuretics are given if there is ascites or edema.

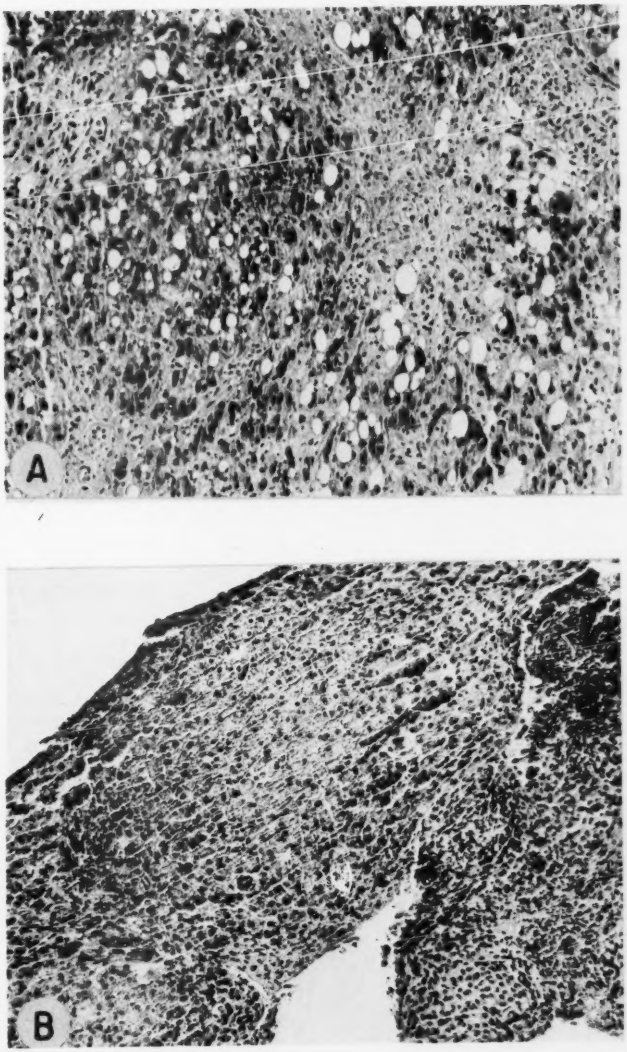



**Fig. 4.** Case 4. A, Needle biopsy specimen on August 24, 1948, showing an extensive fatty infiltration of the hepatic parenchyma with a moderate increase in periportal fibrous tissue; magnification x 100. B, Needle biopsy specimen obtained at the time of cholecystectomy on January 26, 1950. The same amount of connective tissue in the portal areas is present, but the fat globules in the hepatic cells have disappeared; magnification x 100.

## Comment

The lack of choline, as well as of protein and vitamin-B complex in the diet, may produce infiltration and subsequently cirrhosis in rats; this change can be reversed by the administration of choline if fibrosis has not already occurred.[8] Consequently, choline and other lipotropic agents have been employed in the treatment of patients with liver disease. Histologic and other studies on the effectiveness of choline and other lipotropic agents in humans have not been in agreement. Morrison,[17] Franklin and associates,[18] Beams and Endicott,[19] and Fagin, Sahyun, and Pagel,[20] believed from their studies that lipotropic substances including choline, cystine, and methionine, exerted a beneficial effect upon the clinical course of fatty infiltration of the liver. Studies by Cornatzer and Cayer[21,22] suggested that an insufficient supply of lipotropic material was present in *untreated* cirrhotic patients.

Others have reported beneficial effects on the clinical course of cirrhosis and fatty infiltration of the liver without the use of lipotropic substances. Volwiler, Jones, and Mallory,[23] Buck,[24] Klatskin and Yesner,[25] Eckhardt and associates[26] and Seife, Kessler and Lisa[27] have shown that a nutritious diet is beneficial and is associated with effective lipotropism. Choline added to the diet was found to have no additional effect. Post and associates[28] have shown on the basis of protein intake of 1 gm. per kilogram of body weight, that effective lipotropism occurred within four weeks. The administration of choline was without added demonstrable effect, either on the clinical response of the patient, on the results of liver function tests, or on the histologic appearance of the liver.

A high-protein intake undoubtedly assures that adequate choline (present in the protein) is available, so that supplemental choline is probably unnecessary. Since choline is inexpensive and an excess is not harmful, each of our patients here reported was given supplemental choline or other lipotropic substances to insure an adequate supply.

The exact role of steroidal therapy in the treatment of liver disease, both hepatitis and cirrhosis, is obscured by many conflicting reports. Creutzfeldt and Kühn[29] reported cortisone or prednisone to be of benefit to 26 of 40 patients with enlarged livers (hypertrophic cirrhosis or fatty liver). One of our patients (case 1) was given steroidal therapy (Decadron) with apparent benefit.

## Prognosis

The outlook for the patient with fatty infiltration in the liver is excellent with adequate treatment. The decrease in the size of the liver, the improvement in results of liver function tests, the clinical improvement, and the actual decrease in the amount of fatty infiltration in the liver in the four cases cited are typical of the favorable response of patients with fatty livers to adequate treatment. There is little that can be done for fibrosis or scarring that has already occurred in a

cirrhotic liver; however, much can be done for the patient who primarily has fatty infiltration of the liver with little fibrosis. The prognosis is excellent.

## Summary

Fatty infiltration of the liver and cirrhosis have been produced experimentally in animals by dietary deficiencies in protein, vitamin-B complex, or choline. The progress toward cirrhosis is reversed by the administration of choline. The application of these studies to the cause and the treatment of cirrhosis in man is obviously desirable, but remains unproved.

Four case histories of severe fatty infiltration of the liver have been presented. Each patient was an alcoholic and was thought to have a nutritional type of cirrhosis. Treatment consisted of avoidance of alcohol, a high-protein and high-calorie diet, supplemental measures including vitamin B to increase the caloric intake, lipotropic agents, and any special measures indicated by the specific findings on the individual patient. All measures that were considered to be of possible benefit in increasing the protein and caloric intake were used.

Treatment in each case resulted in clinical improvement, a decrease in the size of the liver, improvement in results of the liver function tests, and a disappearance of the fat from the liver as shown by serial specimens of needle biopsies. Fibrosis that had already occurred (in cases 1, 3, and 4) persisted despite therapy.

Severe fatty infiltration of the liver may produce all the signs and symptoms of liver failure, including jaundice and ascites. The prognosis, with treatment, is excellent.

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# SURGERY FOR CHRONIC DUODENAL ULCER: COMPARISON OF RESULTS WITH VAGOTOMY—POSTERIOR GASTROJEJUNOSTOMY AND WITH VAGOTOMY—HEMIGASTRECTOMY

## Evaluation of a Personal Series of 200 Patients

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IN recent years our understanding of the advantages and the disadvantages of certain standard elective operations for chronic duodenal ulcer has improved. As a consequence, our ability to select the "best" operation for a patient deserving surgery is steadily improving. However, since it is unlikely that a single operation ever will prove suitable for every candidate for surgery for chronic duodenal ulcer, a continuing analysis of results of the various operations currently in use would seem to be in order. The report presented here is an evaluation of a personal series of 200 patients, 100 of whom underwent vagotomy—posterior gastrojejunostomy, and 100 of whom underwent vagotomy—hemigastrectomy for chronic duodenal ulcer, during the years 1950 through 1957. The series is consecutive for the operations performed except as noted in the tables; one patient was lost to follow-up.

### Operations Currently Used

*Partial gastrectomy* for chronic duodenal ulcer probably is still the most widely used operation in the country at large, as it was shown to be in Ohio by a survey[1] performed several years ago. In general, the amount of stomach removed governs the effectiveness of the operation as well as the severity of the sequelae. The more stomach that is removed, the less likely is there to be recurrent ulceration, but the more likely are there to be symptomatic weight-loss and the dumping syndrome.

Hospital mortality rates disclosed in the survey[1] varied from 0 to 7.8 per cent, averaging about 5 per cent for the State of Ohio. A high mortality for an elective operation is the most serious argument against its use. The mortality after partial gastrectomy is unrelated to the amount of stomach removed, since usually it is secondary to technical problems related to the duodenal stump.

*Vagotomy and drainage procedure.* A few surgeons in a few centers have continued to believe in and to perform vagotomy—gastrojejunostomy, or vagotomy—pyloroplasty.[2-5] For many years vagotomy—posterior gastrojejunostomy was the standard operation for chronic duodenal ulcer at the Cleveland Clinic Hospital. When it appeared that there would be a substantial number of patients with recurrent ulceration (more than 10 per cent) some of whom would require another operation, we shifted to vagotomy—hemigastrectomy. Evidence presented in this

paper concerning both relative mortality rates (inevitably greater in vagotomy—hemigastrectomy) and the current status of the patients, influenced us to turn to vagotomy—pyloroplasty as a standard operation. It may be stated that the mortality rate for drainage procedures (1.7 per cent for the State of Ohio[1]) is lower than that for gastrectomy and that there is no postoperative problem of severe malnutrition. On the other hand, a recurrent ulceration at the anastomotic margin or in the duodenum or the stomach is more frequent than after gastrectomy, and some patients will require a partial gastrectomy at a second operation.

*Vagotomy with gastric resection* has been pioneered by several surgeons,[6-8] and was used by us as the standard operation for a number of years. It has proved to be the most effective operation against recurrent ulcer, as the study of Herrington and associates[9] recently has shown conclusively. This study renders obsolete an extensive resection of the stomach with its undesirable aftereffects, but the basic risk to life of gastrectomy remains, and undoubtedly patients will be lost who might have lived if a simple procedure without resection had been used.

*Other operations. Vagotomy alone* has no place as the sole surgical procedure to treat chronic duodenal ulcer, since postoperative obstruction and retention with possible nonhealing of the ulcer are entirely too prevalent. *Gastrojejunostomy alone* may be rarely employed in older patients with low gastric acidity and "burnt-out" ulcers where obstruction is the chief indication for surgical intervention. Most surgeons today will prefer to add vagotomy to this procedure. *Pyloroplasty alone* will be performed when a surgeon seeking an ulcer finds none, and hence it will not be therapy for an ulcer. (If he finds one, he should perform vagotomy also.) Other procedures such as the *tubular resection* have not been widely used.

## A Personal Series

Since 1950 I have conducted a "forward" follow-up of all patients operated upon by me for chronic duodenal ulcer, starting at the time of operation and continuing it "forward" to the death of the patient. The advantages of comparisons within a personal series are obvious: selection of patients, operative technic, and evaluation are standardized. Likewise, the ease with which an individual's bias may be perpetuated in a personal series is obvious. The reader is invited to make the necessary allowances for possible bias.

*Procedures.* Three procedures have been used as routine or standard operations from 1950 to the present:

| | |
|---|---|
| 1950 through 1952: | Vagotomy—posterior gastrojejunostomy (Series A) |
| 1953 through 1957: | Vagotomy—hemigastrectomy (Series B) |
| 1958 to the present: | Vagotomy—Heineke-Mikulicz—pyloroplasty (with the one-layer technic of Weinberg and associates[4]) |

None of the procedures listed has been used in a given period to the absolute exclusion of other procedures. For example, the partial gastrectomy without

vagotomy has been the usual emergency operation for massive hemorrhage. A gastric resection has been performed with or without vagotomy in a patient whose ulcer lay very near the pylorus and there was uncertainty as to whether it was a gastric or a duodenal ulcer. Gastric resection has also been performed in a patient in whom a gastric ulcer and a duodenal ulcer coexisted. During the later period when vagotomy—hemigastrectomy was the procedure of choice, vagotomy and a drainage procedure were unhesitatingly used in patients who were poor risks or in whom local inflammation appeared to render resection hazardous. *Table 1* lists the number of each type of operation performed during each period.

**Table 1.**—*Types of surgical procedure used for duodenal ulcer (excluding acute perforation) in 1950—1957*

| Surgical procedure | Number of patients |
|---|---|
| Years, 1950—1952 | |
| Vagotomy—posterior gastrojejunostomy* (Comprises Series A) | 100 (88%) |
| Vagotomy—partial gastrectomy | 5 |
| Partial gastrectomy | 9 |
| Total | 114 |
| Years, 1953—1957 | |
| Vagotomy—hemigastrectomy† (Comprises Series B) | 100 (69%) |
| Vagotomy—posterior gastrojejunostomy | 35 |
| Partial gastrectomy | 7 |
| Vagotomy—pyloroplasty | 2 |
| Total | 144 |

*No deaths in Series A.
†Two deaths in Series B.

*Mortality and follow-up.* Excluded from the mortality statistics for elective operations were any deaths following emergency surgery. (Patients surviving urgent or emergency procedures, on the other hand, have been included in evaluating late results.) Too little time has elapsed to permit evaluation of results of vagotomy—pyloroplasty, although early results suggest that they will be similar to those of vagotomy—posterior gastrojejunostomy. *Tables 2* and *3* give data on the survival and follow-up of patients.

*Criteria.* Two main classifications are used to analyze results: (1) "failure-at-

**Table 2.**—*Vagotomy—posterior gastrojejunostomy for chronic duodenal ulcer: follow-up periods for 100 patients*

*(No patient was lost to follow-up; three patients were excluded from this series.*)*

| Number of years postoperatively | Number of patients | |
|---|---|---|
| | Living | Dead |
| (Hospital death) | — | 0 |
| 1 | 0 | 1 |
| 2 | 0 | 2 |
| 3 | 0 | 1 |
| 4 | 1 | 3 |
| 5 | 0 | 1 |
| 6 | 12 | 0 |
| 7 | 29 | 2 |
| 8 | 35 | 0 |
| 9 | 13 | 0 |
| Total | 90 | 10 |
| Grand total | 100 | |

*To compensate in the series for the three patients who were excluded from follow-up, the next three consecutive patients who underwent vagotomy—posterior gastrojejunostomy (nos. 101, 102, and 103) were added to this series to complete the group of 100 patients. The three patients were excluded because: one patient underwent gastric resection (for gastric retention) in the immediately postoperative period; one patient died from carcinoma of the gallbladder within one year; one patient died from hepatic cirrhosis within one year.

any-time," and (2) "current status." Poor results in the "failure-at-any-time" group include every patient who *at any time* after operation gave evidence of a recurrent ulcer, required another operation, or was dissatisfied with his operation. By way of contrast, in the "current status" group, good results include every patient who is satisfied with his digestive system *at the time of the most recent follow-up*, even if at some time previously there was evidence of a recurrent ulcer, or a second operation was required, or the patient now uses medication or must follow a diet.

*"Failure-at-any-time"* results are grouped as follows. Good result: the patient is asymptomatic or has minimal digestive or nutritional disturbance that does not interfere with his daily schedule of living; the patient is satisfied with the result.

**Table 3.**—*Vagotomy—hemigastrectomy for chronic duodenal ulcer: follow-up periods for 100 patients*

*(One patient was lost to follow-up;* no patient was excluded from follow-up.)*

| Number of years postoperatively | Number of patients | |
|---|---|---|
| | Living | Dead |
| (Hospital death) | — | 2 |
| 1 | 3 | 1 |
| 2 | 17 | 1 |
| 3 | 19 | 1 |
| 4 | 19 | 1 |
| 5 | 22 | 0 |
| 6 | 10 | 0 |
| 7 | 2 | 0 |
| 8 | 1 | 0 |
| 9 | 1 | 0 |
| Total | 94 | 6 |
| Grand total | 100 | |

*To compensate in the series for the one patient who was lost to follow-up, the next patient who underwent vagotomy—hemigastrectomy (no. 101) was included to complete a series of 100 patients.

Poor result: failure has occurred at any time, because of (1) proved recurrent ulcer, (2) one or more hemorrhages, (3) symptoms of ulcer without proof of ulcer, (4) dissatisfaction of the patient.

*"Current status"* results are grouped as follows. Good result: the patient is satisfied at present and has minimal or no digestive or nutritional disturbance and no interference with his daily schedule of living. (The patient may have had a second operation, or be under treatment for a recurrent ulcer.) Poor result: the patient is consistently dissatisfied or has symptoms or an ulcer out of control.

In either the "failure-at-any-time" or the "current status" concept a result may be *equivocal* or uncertain if: (1) other diseases exist which may yield overlapping symptoms. For example, a patient died of cirrhosis of the liver within two years of operation; no recurrent ulcer was proved but the patient was a nutritional cripple; advanced cirrhosis precluded adequate evaluation. (2) The patient is neither fully satisfied with the result nor is he leading a handicapped life, yet a recurrent or persisting ulcer is not proved.

## Comparison of the Two Operations

It is clear from the data already given that the duration of the follow-up for the patients who underwent vagotomy—hemigastrectomy (Series B) is much shorter, on the average, than the follow-up for the patients who underwent vagotomy—posterior gastrojejunostomy (Series A). If past experience is any clue, the longer a series of patients is followed after operation for duodenal ulcer, the greater is the number of late ulcers that develop. From this standpoint, comparison should favor the results of the more recent series of patients who underwent vagotomy—hemigastrectomy, in which the median duration of follow-up is shorter.

*"Failure-at-any-time."* Data for both series are presented in *Table 4.* The

**Table 4.**—*"Failure-at-any-time"* in relation to 200 patients in Series A and Series B who underwent surgery for chronic duodenal ulcer*

| Status of patient | Number of patients | |
|---|---|---|
| | Series A | Series B |
| | Vagotomy—posterior gastrojejunostomy | Vagotomy—hemigastrectomy |
| Died in the hospital | 0 | 2 |
| Second operation | 9 | 1 (Bile gastritis ?) |
| (Ulcer—4) | | |
| (No ulcer—3) | | |
| ("Gastrojejunitis"—1) | | |
| (Dumping syndrome—1) | | |
| Recurrent ulcer, no operation | 9 | 1 |
| Unsatisfactory, no ulcer | 9 | 10 |
| Equivocal | 4 | 10 |
| Too complicated to evaluate | 1 | 2 |
| Total | 32 | 26 |
| Always good result | 68 | 74 |
| Grand total | 100 | 100 |

*See text, pages 172-173 for explanation of term.

following points are noteworthy: (1) 2 deaths in the hospital in the vagotomy—hemigastrectomy group; (2) 9 secondary operations (all patients living) in the vagotomy—posterior gastrojejunostomy group, and 1 in the vagotomy—hemigastrectomy group; (3) 13 presumptive recurrent ulcers in the vagotomy—posterior gastrojejunostomy group compared with one recurrent ulcer in the vagotomy—

hemigastrectomy group, (4) a larger "equivocal" group with resection than with gastrojejunostomy. (Surgeons who follow both types of patients have noted that when a patient represents a good result after vagotomy—posterior gastrojejunostomy he may be completely free of symptoms of "gastric consciousness." The patient who has part of the stomach resected is not so likely to be symptom-free, and he feels well only in comparison with the discomfort he had experienced from the ulcer.)

The patient listed in the result category as "too complicated to evaluate" in Series A, died five years postoperatively of cirrhosis of the liver after four satisfactory years. In one patient in Series B, tuberculosis developed from which he subsequently recovered, and one patient was treated in a mental hospital for a psychotic episode (with vomiting) from which he subsequently recovered.

*Current status.* Data for both series are presented in *Table 5.* In Series A, 19

**Table 5.**—*Current status of 200 patients in both Series A and Series B who underwent surgery for chronic duodenal ulcer*

| Current status | Number of patients | | | |
|---|---|---|---|---|
| | Series A | | Series B | |
| | Vagotomy—posterior gastrojejunostomy | | Vagotomy—hemigastrectomy | |
| Died in the hospital | | 0 | | 2 |
| Always satisfactory | | 68 | | 74 |
| Living | 59 | | 70 | |
| Died of other disease | 9 | | 4 | |
| Satisfactory after initial failure | | 19 | | 8 |
| Total currently satisfactory | | 87 | | 84 |
| Consistently unsatisfactory | | 7 | | 7 |
| Equivocal | | 4 | | 8 |
| Too complicated to evaluate | | 2 | | 1 |
| Total doubtful or unsatisfactory | | 13 | | 16 |
| Grand total | | 100 | | 100 |

patients have recovered from temporary setbacks; some of these patients required another operation. It is noteworthy that seven patients in each series—none with proven ulcer—have had consistently poor results. It is probable that psychologic and constitutional factors beyond the reach of surgery are at work in these patients. The fact that the "equivocal" group is larger in Series B than in Series A reflects the higher incidence of nutritional problems and "gastric uncertainty" that follows partial gastrectomy.

## Discussion

The findings in the personal, consecutive series comparing 100 patients who underwent *vagotomy—posterior gastrojejunostomy* and 100 patients who underwent *vagotomy—hemigastrectomy* indicate that the end results are not different if one chooses to judge by the current clinical status of the patients. Only one patient has been lost to follow-up, which for the most part has been conducted by annual mimeographed questionnaires mailed to the patients.

Since *vagotomy—posterior gastrojejunostomy* was the standard operation for several years before we changed to *vagotomy—hemigastrectomy,* the follow-up for the former group is longer—a median of eight years among 90 living patients, as compared with a median of four years among 94 living patients in the second group. The significant findings appear to be the following: (1) there were two deaths in the hospital in the group who underwent resection, compared with all surviving in the group who underwent gastrojejunostomy. (2) The total numbers of patients currently satisfied in each group are about the same. (3) Nine patients who underwent gastrojejunostomy came to a second operation, which was a resection in each of eight patients. Ulcers were found in four patients and gastrojejunitis in one patient. All but one of these patients are now satisfied with the results. (4) Only one patient who underwent primary resection required a second operation: conversion of a gastrojejunostomy (Billroth II) to a gastroduodenostomy (Billroth I). (5) There are 13 patients who underwent posterior gastrojejunostomy in whom recurrent ulceration presumably developed. In most of these, symptoms were transitory and responded readily to simple measures that had proved inefficacious before operation. (6) There was only one patient who underwent vagotomy—hemigastrectomy in whom an ulcer recurred.

## Conclusion

Vagotomy—posterior gastrojejunostomy is a safer operation for chronic duodenal ulcer than is vagotomy—hemigastrectomy. If one accepts the fact that in an appreciable proportion of patients (13 per cent in this series) evidence of recurrent ulceration will develop at some time, and a few patients (9 per cent in this series) will come to a second operation, vagotomy—posterior gastrojejunostomy is a valuable procedure and should be used in preference to gastric resection in (1) poor-risk patients, or (2) in patients in whom there is an inflammatory mass or other technical hazards that increase the surgical risk.

The effectiveness of vagotomy—hemigastrectomy against recurrent ulceration, highlights the obvious conclusion that larger amounts of stomach need never be removed in treating chronic duodenal ulcer.

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# THE EARLY DETECTION OF PELVIC CARCINOMA — METHODS AND THEIR LIMITATIONS

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EARLY detection of pelvic carcinomas is not a guarantee of the eradication of such tumors, but nevertheless is highly desirable. The effectiveness of treatment is dependent not only on the stage of the disease when treatment is instituted, but also on the response of the tumor to varieties of treatment, and the invasiveness or ability of the tumor to replace normal host tissues. Some tumors already have metastasized when the primary lesion is small and otherwise would be considered favorable for treatment.

Because early diagnosis generally will improve survival rates, the American Cancer Society and other interested agencies have conducted intensive educational campaigns directed at the layman as well as at the physician. A great quantity of literature directed at the public, points out the desirability of frequent and regular examinations for cancers. The medical literature contains a multitude of reports pertaining to various methods of detection. As a result, many women are having yearly pelvic examinations. Despite these efforts there are many misconceptions regarding the whole problem of cancer detection. The laity is prone to look on the diagnosis of cancer as a problem with a precise answer, and to expect all physicians to have the facilities for full and complete detection of cancer. In some instances, people seem to regard the detection process as simple as dropping a coin in a penny scale and obtaining a weight and fortune. The answer to malignant disease is not so easily obtained.

It is unfortunate that physicians in some regions do not have adequate facilities available for pathologic study. Consequently, cytologic or histologic reports may be incomplete or misleading. Incorrect diagnoses may result, and some patients may be treated for cancers they do not have, or may be given clearance for cancers that actually are present. In view of this confusion, it is well for the physician to reconsider what can be expected from various available detection methods and to recognize the limitations in their use.

## Defining the Problem

What is the relative incidence of the several types of gynecologic cancer? In terms of survival rates, which anatomic sites present the most favorable prognosis following treatment? Randall and Gerhardt[1] have estimated that gynecologic malignancy can be expected to develop in approximately 10 per cent of all women. The occurrences of cancer of the cervix and the body of the uterus are three and one-half times more frequent than are the combined occurrences of ovarian and of vulvar carcinoma. The incidence of vaginal and of tubal carcinoma is small.

The early detection of malignancy is dependent upon the site of involvement, since, if lesions can be visualized and specimens can be easily obtained, diagnostic studies are more easily performed. The cure rate does not necessarily follow this pattern, since there are variations in individual tumors: though the cervix is visible, carcinoma of the body of the uterus is more amenable to treatment than is cervical carcinoma. Randall[2] reported cancer mortality rates, covering a period of 20 years according to specific age groups and to anatomic sites, in females in New York State. Over this period, the mortality rates for cancer of the breast remained unchanged. Mortality rates for uterine cancer decreased 10 per 100,000 women, and ovarian cancer mortality rates increased 4 per 100,000 women.

Although the ovary is less accessible for diagnosis, it also may represent neoplastic behavior similar to that in the breast. In spite of the accessibility of the breast for examination, survival rates from cancer of the breast have not improved in a considerable number of years. It is probable that even if the ovaries were superficially located, mortality rates would be unchanged. The increase in incidence of ovarian carcinoma in large part is due to better diagnosis and a population with increasing longevity.

Present detection methods may be grouped into clinical and pathologic phases. The clinical methods are confined to evaluation of history, inspection, and palpation. These procedures do not establish the diagnosis, but are helpful in indicating the need for histologic examination. Pathologic examination of cell (cytology) and of tissue specimens is of the utmost importance; the former in screening patients and the latter in establishing diagnoses.

## History

The importance of the patient's history depends upon the particular site where cancer might be found. The history is of maximal value in endometrial carcinoma and of the variable value in vulvar and cervical carcinoma. The history is of practically no value in detecting ovarian carcinoma, because this tumor generally is silent, producing no distinct symptoms until it is extremely far advanced.

Sporadic bleeding or mucous vaginal discharge generally will occur in the presence of carcinoma of the endometrium at a time when the tumor may be completely controlled by available methods of treatment. This is in large part due to the fact that cancer of the body of the uterus remains localized for a considerable period of time and bleeding occurs secondary to local overgrowth and necrosis of neoplastic tissue.

A history of long-standing vulvar pruritis, a painful lesion that has failed to heal, or a remote history of irradiation treatment for vulvitis certainly should arouse the suspicions of the examining physician as to the presence of vulvar carcinoma.

In years past, the symptoms of cervical carcinoma were thought to be of great importance. These symptoms consist of bleeding that is painless, progressive, and prone to follow trauma. New and unusual vaginal discharge may also be important. Unfortunately, these symptoms may occur only when a tumor is in an advanced stage, and it is for this reason that regular pelvic examinations are of great importance even in the absence of symptoms.

## Inspection

Inspection is of value only in the detection of vulvar and cervical lesions. It is of less importance in cervical lesions, since, if inspection were to be depended upon, approximately 90 per cent of the cervical carcinomas in situ, which are microscopic, would be overlooked. Inspection of the vulva is of great importance, and should constitute the first step in a well-ordered pelvic examination. Unfortunately, the physician oftentimes overlooks the vulva and proceeds directly to the examination of the cervix and the vagina. Greater attention to the vulva on routine examinations would improve the rate of early detection of vulvar lesions.

Carcinoma in situ and invasive carcinoma of the cervix are often associated with otherwise benign cervical lesions; consequently, the presence of a cervical erosion, polyp, laceration, eversion, or chronic cervicitis indicates the need for establishing histologically the presence or the absence of invisible carcinoma in situ or of invasive carcinoma.

Colposcopy has been suggested as an aid to better evaluation of the cervix. Scheffey, Lang, and Tatarian[3] have reported that in 168 patients colposcopy did not result in the primary diagnosis of a single case of malignancy nor did it result in differentiation between carcinoma in situ and early invasive carcinoma. It is true that colposcopy may complement cytologic examination by indicating the sites where biopsy specimens should be taken. Colposcopy is a research tool and seems unlikely to become widely used or necessary for early detection of cancer.

## Palpation

Palpation is of importance in diagnosing ovarian caricinoma, but it is of little or no value in identifying malignant lesions at sites other than the ovaries. Unfortunately, when suspicious ovarian enlargements are found, they may represent far-advanced cancer. A cyst 7 cm. or larger in size, which persists in a young woman, should be investigated. In women at or near the menopause, considerable caution is indicated. Any persistent ovarian enlargement should be investigated promptly. A good precept is that a palpable ovary in a postmenopausal woman denotes the presence of carcinoma until proved otherwise.

## Cytologic Studies

Cytologic studies have become widely used in the last 10 years and patient

demand for them is increasing. This demand has occurred despite an original concern by clinicians in regard to the cost of cytologic studies, and because of the high rate of reliability, as confirmed by well-controlled and large series that have been reported. Unfortunately, there is considerable variability in results and accuracy in many parts of the country. When accuracy is not dependable, it is better not to carry out such studies; standard quadrant biopsy of the cervix is preferable. A high rate of false-positive reports leads to needless alarm and to many unrewarding diagnostic studies. A high rate of false-negative reports may lead to an unwarranted sense of security and to the clinician's overlooking of lesions that should be found.

The methods of obtaining cytologic specimens vary considerably over the country. These have consisted of a great variety of implements and materials ranging from applicator sticks, tongue blades, spatulas and aspirating pipets, to Gelfoam and tampons. Most pathologists have preferences that should be observed by the clinicians. It is our procedure to use a single cotton applicator stick that is rolled over the surface of the cervix and into the external os.[4]

Four people are involved in cytologic accuracy: the patient, the clinician, the technician, and the pathologist. Patients are prone to take douches just before having a pelvic examination unless advised not to. Such a practice may be responsible for false-negative results, since diagnosis is dependent on exfoliated cells. The clinician is responsible for providing a well-prepared slide or slides for interpretation by the pathologist. The technician must be well trained in staining and in screening specimens, and the pathologist must have a breadth of experience enabling him to interpret the slides properly. The clinician is ultimately responsible for making a clinical application of the information obtained. When numerous persons handle specimens there is a continuing chance that wrong identifications may occur.

Several principles are important in the interpretation and clinical application of cytologic studies. First, these studies are screening in nature and serve to indicate those patients who require more complete investigation. These studies are not diagnostic, and therapy should not be started without a histologic diagnosis. Secondly, a positive cytologic report should not be ignored. Cytologic studies may be likened to the sport of fishing: when no fish is caught, it does not rule out the presence of fish, but when a fish is caught, we are generally convinced that other fish are present. When abnormal cells are found, we must assume that there is a source for them and efforts should be made to find that source. If a second cytologic study is done and is negative for neoplastic cells, it does not negate the first result.

Cytologic studies may be of value in detecting any gynecologic malignancy; however, its greatest value lies with the early detection of cervical abnormalities. When the standard cervical technic is used for the detection of endometrial

carcinoma, the accuracy drops to about 80 per cent as opposed to a better than 90 per cent accuracy in the detection of cervical carcinoma. Endometrial-aspiration spreads are of value only when they are positive for atypical cells. A negative cytologic report is of no value, particularly when clinical symptoms are present. An occasional ovarian carcinoma can be detected by either cervical or endometrial cytologic technics.

## Biopsy

Biopsy is the only available method of confirming clinical impressions derived from the application of any of the above-outlined technics. Excisional biopsy should be performed on any suspicious vulvar lesions, such as those that are ulcerated or that fail to heal in a short time under active medical treatment. When a cervical lesion is present it should be biopsied before cauterization or any other treatment. This generally can be performed in the office, causing little or no pain to the patient and minimal inconvenience to the doctor.

Endometrial biopsies obtained in the office are of value only when the specimens are positive for carcinoma. Biopsies may be desirable if frozen-section diagnosis is not available, or if radium is not used as part of the treatment of endometrial carcinoma.

An ovarian biopsy requires laparotomy, and the clinician must be well versed in the gross pathologic features of ovarian carcinoma and be ready at the time of operation to make a decision regarding appropriate therapy. Under ideal circumstances, a pathologist is available for providing frozen-section diagnoses. An evaluation of diagnostic aids is summarized in *Table 1.*

**Table 1.**—*The early detection of pelvic malignancy—evaluation of diagnostic aids*

| | Site of carcinoma | | | |
|---|---|---|---|---|
| Diagnostic aids* | Cervix | Corpus uteri | Ovary | Vulva |
| History | ± | + | 0 | ± |
| Inspection | ± | 0 | 0 | + |
| Palpation | 0 | 0 | ± | ± |
| Cytology | + | ± | 0 | + |
| Office biopsy | + | + | 0 | + |
| D and C | + | + | 0 | 0 |

* + means generally helpful; ± of variable help; 0 of no value.

## Specific Application of Cytologic Technics

Our cytologic results are reported according to the original Papanicolaou classification with various subgroupings. Diagnostic methods depend on the gross appearance of the cervix and the cytologic classification: classes I and II are essentially normal and require no treatment. A gross cervical lesion should be biopsied. If the biopsy specimen is negative for carcinoma, cautery or conization should be performed to eliminate the cervical lesion. When the cervix is clean, a yearly cytologic study should be done. Spreads of cytologic class III represent findings that are too important to disregard but not serious enough for immediate concern if the cervix is clean. Another spread should be obtained in three months. If the cervix presents a gross lesion, biopsy and cautery or conization should be performed for more complete diagnosis and treatment. The cervix should be examined periodically (including cytologic studies) after the completion of healing.

Classes IV and V spreads demand intensive diagnostic study. In both of these classes, a biopsy is done if there is a visible cervical lesion. If the biopsy reveals no invasive carcinoma, a sharp-knife and cautery conizations *(Fig. 1)* with incidental dilatation of the cervix and curettage (D and C) are performed. When no lesion is visible, sharp-knife and cautery conizations are done without further study. Conization specimens are subjected to step-block examination *(Fig. 2)* so that the whole specimen is examined as thoroughly as is feasible.

A random or quadrant biopsy that reveals chronic cervicitis, rules out nothing. Scott and Reagan[5] have demonstrated the high incidence of endocervical carcinoma in situ when the squamocolumnar junction is negative for this lesion. On the other hand, a biopsy that reveals carcinoma in situ does not rule out the presence of invasive carcinoma. We know that these two lesions coexist and that finding one does not rule out the presence of the other. Therapy for carcinoma in situ is grossly inadequate for invasive carcinoma.

When histologic examination fails to demonstrate the source of abnormal cells, it may mean that the lesion has been removed but was not found in the examined tissue, or, more importantly, the lesion may have been overlooked completely and still be present. Thus, when the cervix has healed, follow-up cytologic study should be carried out. If negative for abnormal cells, these studies should be done at three-month, at six-month, and thereafter at yearly intervals. If cytologic studies are persistently positive, a second conization and dilatation and curettage should be performed. If the lesion is still not demonstrated, cytologic follow-up is indicated. If positive spreads persist, exploration and hysterectomy should be advised because abnormal cells may be produced by the ovaries or the tubes. The percentage of false-positive cytologic reports largely depends on the persistence of the clinician and the pathologist. Our false-positive incidence is 4 per cent in 22,716 cytologic specimens. Thus, when a positive report is obtained, there is only one chance in twenty-five of its being unexplained. Patients having

unexplained positive cytologic reports before D and C and conization, and normal reports thereafter, may either have had a micro lesion removed or, if none was present, be spared future trouble because of the prophylactic benefit derived from conization.

The technic of conization is of great importance. It has previously been detailed.[6] In summary, the procedure should always be done under anesthesia. The vaginal preparation should be gentle with as little trauma to the cervix as possible. A No. 10 Bard-Parker blade is used for the conization, employing a sawing motion in a Scanzoni-like maneuver. Care should be taken to avoid

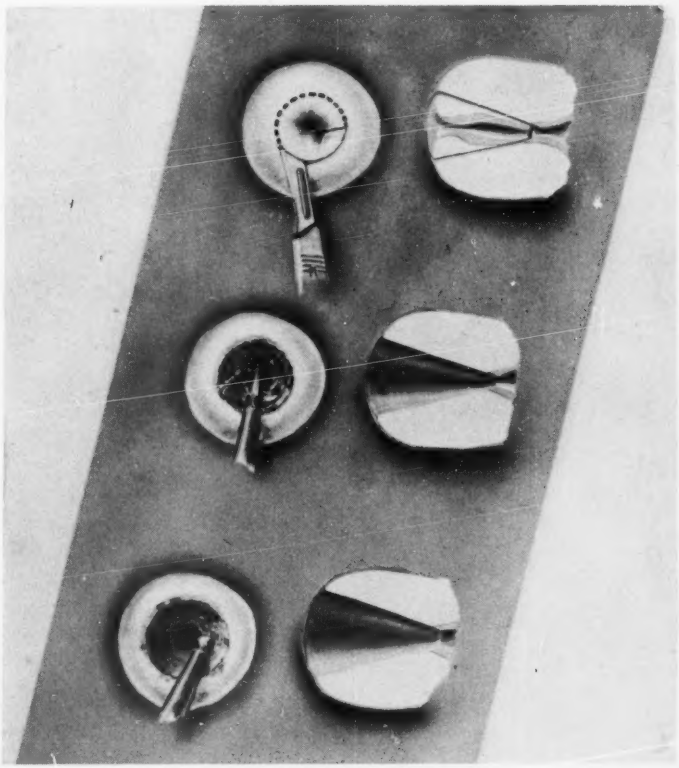

**Fig. 1.** Drawing showing sharp-knife conization (top), cautery conization (middle), and ball-point cauterization (bottom). In each series the end-on view is left, the longitudinal section is right. (From Krieger, J. S., and McCormack, L. J.: Surg. Gynec & Obst. 109: 328-332, Sept. 1959; by permission of SURGERY, GYNECOLOGY & OBSTETRICS.)

needless laceration of the cervix and to obtain as large a specimen as is practicable. Efforts should be made to extend the conization as close to the internal os as possible. A Heyman loop is used for cautery conization immediately after the sharp-knife procedure. It is believed that this improves the appearance of the healed cervix and is of value in controlling bleeding. Final hemostasis is obtained with a ball-point cautery.

**Fig. 2.** Conization specimens reduced to serial blocks. (From Krieger, J. S., and McCormack, L. J.: Surg. Gynec. & Obst. 109: 328-332, Sept. 1959; by permission of SURGERY, GYNECOLOGY & OBSTETRICS.)

## Summary

The early detection of pelvic carcinoma depends on the co-operation of the patient, the clinician, and the pathologist. Women are being educated to have regular pelvic examinations. Detection methods comprise both clinical examination and pathologic studies. The diagnostic methods available in the detection of pelvic malignancy are tabulated briefly. Our most encouraging results, in early diagnosis, occur when multiple diagnostic methods are available, particularly for the cervix and the endometrium; ovarian carcinoma can be detected early only by chance. Vulvar carcinoma can be diagnosed earlier and more frequently than occurs now, if physicians will look for such lesions.

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# CARDIAC DISEASE SECONDARY TO POSTNEPHRECTOMY ARTERIOVENOUS FISTULA

## Report of a Case

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THE detection of peripheral arteriovenous fistulas should be early, and regardless of cause they should be repaired surgically although they rarely alter the hemodynamics of the central circulation. The diagnosis of this type of peripheral vascular defect usually is not difficult to establish, particularly when the symptoms and abnormal physical findings are localized to an extremity or to superficial areas in other parts of the body. A communication between a renal artery and a renal vein may not be so simple to identify.

Irrespective of the cause, a renal arteriovenous fistula may be present for many years before abnormal cardiac hemodynamic effects are produced or become clinically recognizable. On the other hand, cardiomegaly, congestive heart failure, or a cardiac arrhythmia may develop early if the extracardiac shunt is large. Symptoms and abnormal objective findings referable to the heart may also be attributed to primary cardiac disease, and may go unrecognized as a reversible and so-called "curable" type secondary to another correctible vascular lesion.

A case of a postnephrectomy arteriovenous fistula 17 years after nephrectomy is being reported to present briefly the clinical manifestations and hemodynamics and to emphasize the importance of a complete physical examination as a reliable diagnostic approach in the detection of the extracardiac shunt that should be recognized as an unusual but possible cause of heart disease. One unreported case of a postnephrectomy arteriovenous fistula without secondary cardiac effects has been seen at the Cleveland Clinic.

Scheifley, Daugherty, Greene, and Priestley[1] recently reviewed the literature on 12 reported cases of renal arteriovenous fistula and added three cases. The two cases of postnephrectomy arteriovenous fistulas reported by Schwartz, Borski, and Jahnki,[2] and Muller and Goodwin,[3] and the case reported by Hollingsworth[4] which was not definitely diagnosed were not included in the review because of the absence of hypertension and myocardial insufficiency which Scheifley and associates[1] reported to be the prominent features of a renal arteriovenous shunt with an intact kidney. In the case reported by Muller and Goodwin[3] the patient had severe heart failure, and the case herewith reported represents a predominantly heart problem with myocardial insufficiency and a cardiac arrhythmia. Thus, according to recent reviews of the literature, to date, there are two reported cases of postnephrectomy arteriovenous fistula and a total of 17 cases of renal arteriovenous communication.

## Report of a Case

A 57-year-old white housewife was examined here in August, 1957, because of weakness and loss of weight which she attributed to digitalis that was prescribed by her physician five months previously for an irregular heartbeat. Approximately eight years previously another physician prescribed digitalis because of a "heart condition"; the drug was taken for only a short time and then was discontinued because of nausea and vomiting. For many years she experienced periods of weakness, fatigability, and dizziness that was attributed to labyrinthine vertigo. Palpitation occurred frequently, and about one month prior to examination here, swelling of the feet developed, which responded to the parenteral and oral administration of diuretics. There was no dyspnea, but she had voluntarily limited her activities because of fear of producing "further injury to the heart." There was no history of rheumatic fever, hypertension, or diabetes mellitus. The past history was otherwise unremarkable except for a right nephrectomy performed 17 years previously and a hysterectomy and an appendectomy performed, respectively, 12 years and 25 years previously.

*Physical examination.* The patient appeared to be chronically ill. She was apprehensive but not in acute distress. The temperature was 98 F. orally. The blood pressure was 140/70 mm. of Hg. The skin, eyes, ears, nose, and throat were normal. A funduscopic examination demonstrated only grade I arteriosclerotic changes. The thyroid gland was of normal size, contour, and consistency. No abnormal lymph nodes were present. Examination of the chest revealed the lungs to be clear. The area of cardiac dullness was percussed 11 cm. from the midsternal line in the left fifth intercostal space. The heart rhythm was irregular with a ventricular rate of 120 beats per minute. A striking feature was the forceful heartbeat with a pronounced systolic thrust over the anterior left side of the chest. There was a grade III apical systolic murmur well transmitted over the precordium and to the left axilla. There was no diastolic murmur, gallop rhythm, pericardial friction rub or palpable thrill. The first heart sound at the apex was accentuated while the second sound was unremarkable. Examination of the abdomen elicited a faint thrill in the right upper quadrant in addition to a continuous machinery-like murmur in the same area. The intensity of the murmur was loudest in the right costophrenic angle and was accompanied by an easily palpable thrill. No masses were palpable and no hepatosplenomegaly was present. The abdominal aorta was of normal size and contour, and the peripheral pulses were equal, full, and synchronous. There were no congestive manifestations. Results of a pelvic examination were normal, and no abnormal musculoskeletal disorder was apparent. A neurologic survey was unremarkable.

*Laboratory studies* showed: hemoglobin content 13.5 gm. per 100 ml., red-cell count 4,860,000 per cu. mm., white-cell count 7,200 per cu. mm. with 54 per cent polymorphonuclear cells, 44 per cent lymphocytes, 1 per cent eosinophils and 1 per cent monocytes. Blood Wassermann and Kahn determinations were negative. Blood urea was 43 mg. per 100 ml. A urinalysis was negative except for 15 to 20 pus cells. Fasting and two and one-half hour postprandial blood sugar determinations were respectively 81 mg. and 83 mg. per 100 ml. Antistreptolysin titer was 20 units. A corrected sedimentation rate reading was 0.2 mm. per minute (Ernstene and Rourke method).

Fluoroscopy demonstrated the heart size to be 40 per cent above average. There was multichamber enlargement with increased amplitude of pulsations in the right and left ventricles. The aortic knob appeared slightly enlarged with calcification in the arch. No valvular or pericardial calcification was visualized. The vascular markings were increased but no hilar systolic intrinsic pulsations could be seen. Roentgenograms of the chest *(Fig. 1)* demonstrated essentially the same findings. The preoperative electrocardiogram *(Fig. 2)* showed atrial fibrillation, digitalis effect with QRS complexes in V5 and V6 consistent with left ventricular hypertrophy. A urogram demonstrated the absence of the right kidney, and a normal left kidney. An aortogram was made to define the arteriovenous communication *(Fig. 3)*.

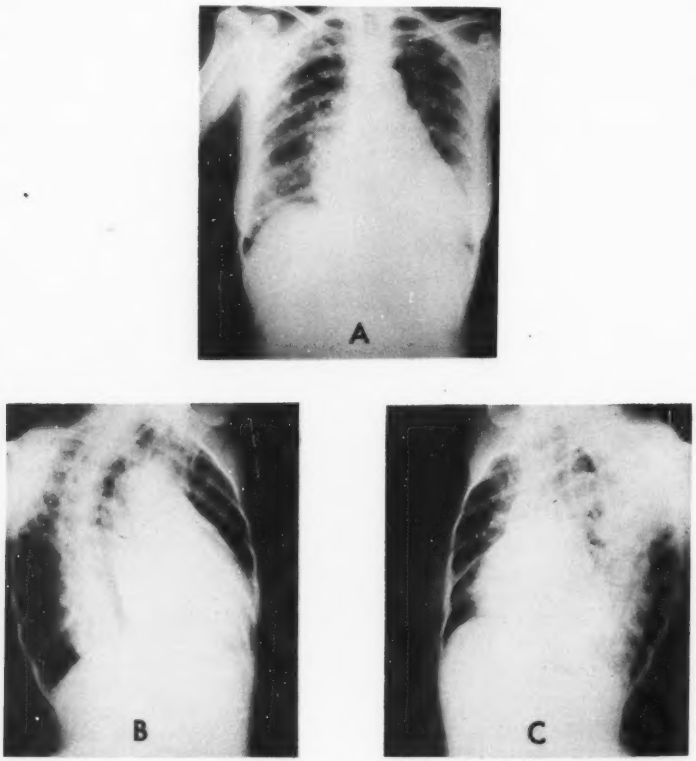



**Fig. 1.** Preoperative roentgenograms of the chest viewed in the (A) posteroanterior, (B) right anterior oblique, and (C) left anterior oblique projections. Note the small amount of calcification in the aortic knob. The transverse cardiac diameter was 16 cm.

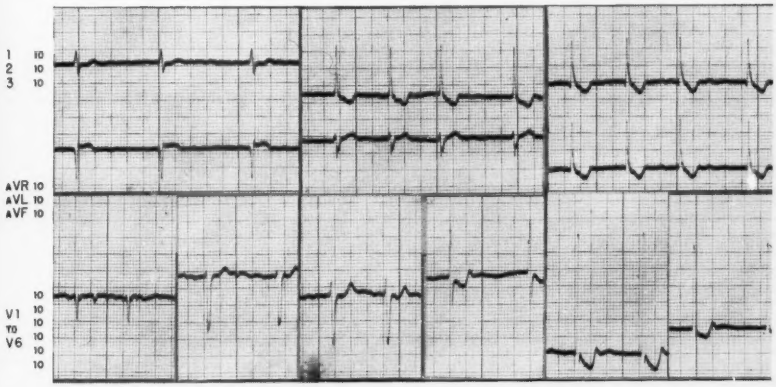



**Fig. 2.** Preoperative electrocardiogram showing atrial fibrillation, and digitalis effect with QRS complexes in V5 and V6 consistent with left ventricular hypertrophy.

The right renal artery was ligated and divided. The aneurysmal dilatation of the renal vein and the inferior vena cava *(Fig. 4),* discovered at surgery, collapsed along with disappearance of a palpable thrill during compression of the right renal artery. There was a slight increase in the ventricular rate at the same time, but there was no change in the basic rhythm. No record of the blood pressure was made immediately after obliteration of the arteriovenous communication, but for the first 12 hours after surgery, blood and levarterenol bitartrate* was administered to raise and to maintain the systemic systolic pressure between 80 and 90 mm. of Hg. During this period the ventricular rate ranged between 110 and 160 beats per minute.

Two weeks after surgery, quinidine was administered and sinus rhythm was restored. At that time fluoroscopy and progress roentgenograms of the chest *(Fig. 5)* demonstrated a significant reduction in heart size and a decrease in the pulmonary vascular markings. The transverse cardiac diameter measured 14.0 cm., compared to 16.0 cm. preoperatively with only 25 per cent enlargement above average for her given height and weight according to the Ungerleider scale. Two months postoperatively the apical systolic murmur was of grade II intensity and the systolic thrust and accentuated first heart sound were absent. Further reduction in heart size had occurred and the transverse cardiac diameter was 13.6 cm. *(Fig. 6).* In addition, a remarkable change had occurred in the electrocardiogram *(Fig. 7);* there was sinus rhythm with no residual evidence of left ventricular hypertrophy.

The patient returned for another progress examination 14 months later (15 months postoperatively). During the interim, her functional status had improved despite numerous emotional problems that continued to curtail many activities. The objective findings, however, were striking. She had gained 20 pounds in weight and she appeared to be in excellent health. Results of the physical examination were entirely negative.

**Levophed (levarterenol bitartrate), Winthrop Laboratories.*

A

B

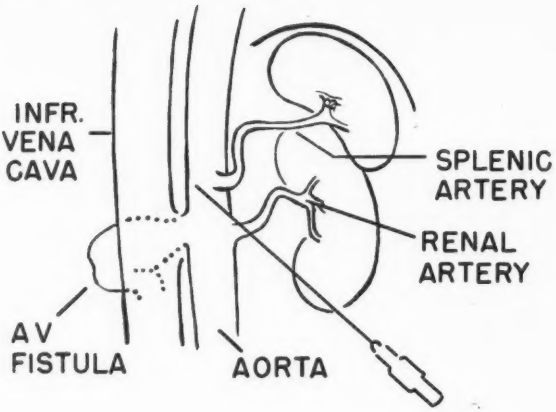



**Fig. 3.** A, Aortogram that demonstrates evidence of the right renal arteriovenous fistula. B, Diagram showing orientation.

A

B

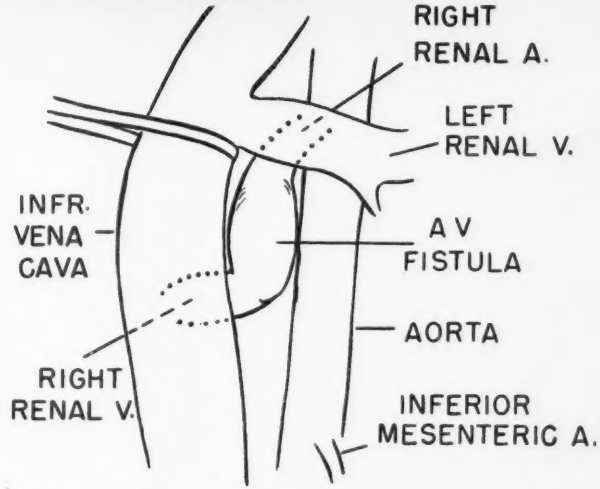



Fig. 4. A, Photograph of anatomic findings at the time of operation before the right renal artery was divided. Note the aneurysmal dilatation of the inferior vena cava. B, Diagram showing orientation.

Sinus rhythm had continued and a murmur was no longer audible. The heart size was average for her height and weight, according to the Ungerleider scale, with a configuration suggestive of minimal left ventricular enlargement *(Fig. 8)*. A third electrocardiogram *(Fig. 9)* demonstrated sinus rhythm with no diagnostic changes. All of the findings were indicative of a normal heart and circulation. In comparison to the tracing in *Figure 7*, the amplitude of the R waves decreased appreciably in leads II, III, AVF, V4, V5, and V6.

## Clinical Features

Despite the development of new and better roentgen equipment and improvement in laboratory diagnostic technics, a detailed history and a complex physical examination remain fundamental with nothing equivalent for the recognition of

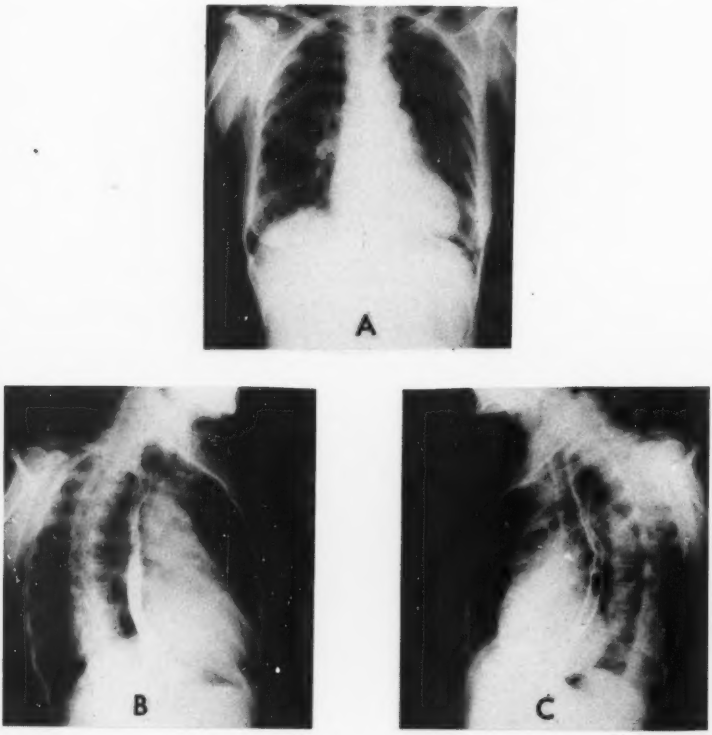
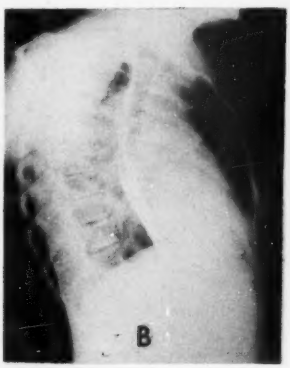



**Fig. 5.** Roentgenograms of the chest two weeks after division of the renal artery. There is moderate left atrial and right-and-left ventricular chamber enlargement. The transverse cardiac diameter was 14 cm.

disease and, in many cases, the establishment of a correct diagnosis. For example, the examination of the heart alone can be misleading, because on the basis of abnormal auscultatory cardiac findings, the diagnosis of primary heart disease may be the only consideration. A general physical examination is mandatory in order to detect or to exclude disorders that secondarily affect cardiac function.

Because of the resultant increase in cardiac output produced by a renal arteriovenous fistula or any extracardiac shunt, cardiomegaly, a cardiac arrhythmia, heart murmur, and congestive manifestations can develop. High output failure results in these cases and always should be considered in a patient who has symptoms and objective evidence of congestive manifestations. Fluoroscopy of the chest can be helpful in recognizing an increase in cardiac output. Cardiomegaly,



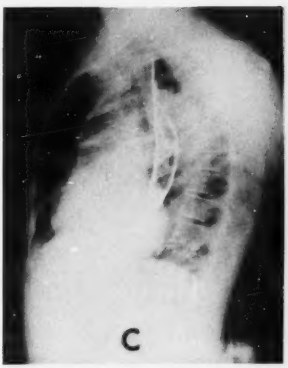




Fig. 6. Roentgenograms two months postoperatively. The transverse cardiac diameter was 13.6 cm.

right ventricular enlargement, increased amplitude of chamber pulsations along with an extremely "hyperkinetic heart" and occasionally multichamber enlargement are the characteristic features. A cardiac arrhythmia, enlargement, and hypertrophy of the ventricular chambers may also be demonstrated by the electrocardiogram.

The murmur of an arteriovenous fistula should be easily recognized. It has been clearly described by Edwards and Levine.[5] The murmur is continuous with a systolic accentuation. In the presence of only a systolic murmur, the possibility of an obstruction of the effluent vein, partial occlusion of the artery resulting in a significant reduction in the arteriovenous gradient, or an arterial aneurysm should be considered.

## Pathologic Physiology

Although peripheral and postnephrectomy arteriovenous fistulas do not produce hypertension, myocardial insufficiency can result if the shunt is of significant magnitude to impose a burden on the myocardium. Although the systemic hypertension associated with a renal arteriovenous fistula with an intact kidney is partially responsible for the development of cardiac enlargement and failure, the size of the artery-and-vein communication and the length of time the fistula has been present are also major factors. For example, the development of congestive heart failure as late as 57 years after the establishment of a peripheral fistula has been reported by Dorney.[6] Muller and Goodwin[3] reported a patient having an arteriovenous fistula with the development of congestive heart failure 29 years after a nephrectomy.

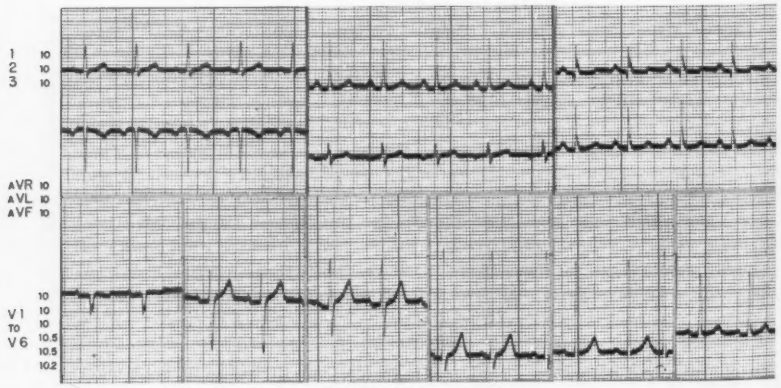



**Fig. 7.** Electrocardiogram two months postoperatively showing sinus rhythm with no evidence of left ventricular hypertrophy.

The physiology of an arteriovenous fistula has been thoroughly studied by Holman.[7] The pressure gradient between a systemic artery and vein which produces a significant left-to-right shunt results in reduced peripheral resistance and, as a compensatory mechanism, cardiac output increases. The increased volume and velocity of flow to the right side of the heart lead to increased heart work, cardiac dilatation, and ultimately cardiac hypertrophy. Congestive heart failure that may subsequently develop may be indistinguishable clinically from congestive manifestations due to primary valvular or myocardial disease, but physiologic studies have found the cardiac output to be decreased and the peripheral resistance to be increased in myocardial failure.

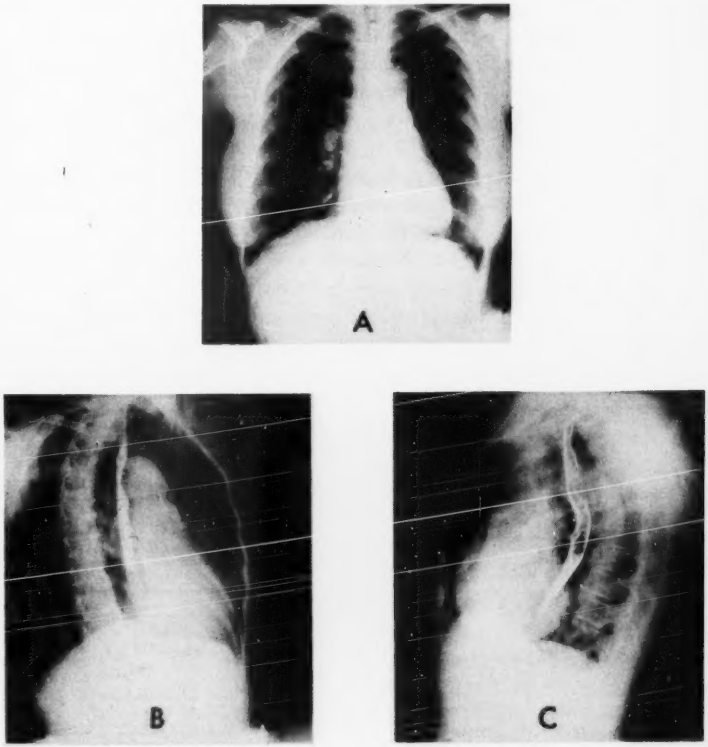



Fig. 8. Progress roentgenograms of the chest 15 months postoperatively. The transverse cardiac diameter was 12 cm.

Youmans's[8] studies on the circulatory effects of closing an arteriovenous fistula showed that there is an immediate elevation of the systemic blood pressure with a concomitant decrease in the pulse rate and the cardiac output. The decrease in the blood pressure and the increase in the heart rate in the case reported here were attributed to loss of blood and to atrial fibrillation.

## Diagnostic Features

With or without cardiac symptoms, a patient demonstrating cardiac enlargement without obvious cause and with a history of an injury or of surgery, should be carefully examined for an arteriovenous fistula. Good standard procedure is to perform auscultation over any area of scar tissue to detect a possible arteriovenous fistula. Fourteen[1-3,9-15] of the 17 cases that have been reported in addition to this case manifested a bruit, and the diagnosis of a renal arteriovenous fistula was established or at least suspected at the time of the physical examination. In two cases,[1,16] the diagnosis was made at the time of surgery. The auscultatory features of a systemic artery-and-vein communication have been discussed. It is fair to assume that in most instances, a careful physical examination is sufficient to detect this vascular defect.

An attempt must always be made to determine whether cardiac enlargement, a cardiac arrhythmia or congestive manifestations are on the basis of primary or secondary cardiac disease.

A careful and complete physical examination is essential for the detection of an extracardiac shunt. Fluoroscopy can be helpful in the recognition of cardiomegaly and increased amplitude of the ventricular pulsations indicative of an increase in cardiac output. Careful observation of the hilar vessels for intrinsic systolic pulsations (hilar dance) is also important in establishing the presence or

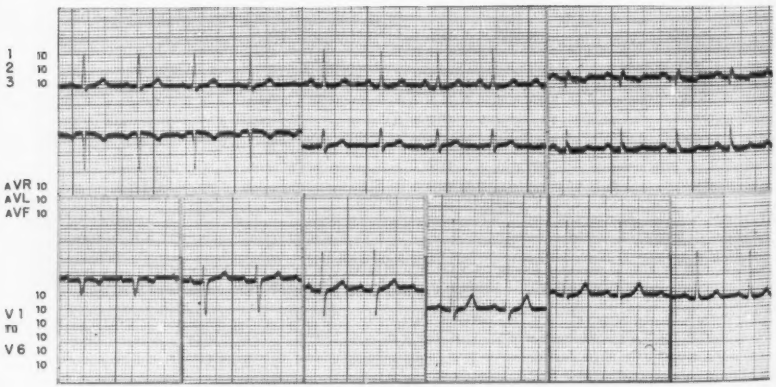



**Fig. 9.** Electrocardiogram 15 months postoperatively showing no diagnostic changes.

absence of a shunt in the central circulation. With the clinical manifestations of an increased cardiac output, hyperthyroidism, anemia, beriberi heart disease, Paget's disease and an intracardiac shunt as mentioned should be considered in the differential diagnosis. The pertinent clinical features of these various conditions will not be discussed at this time but a complete physical examination, fluoroscopy of the chest and a few laboratory studies will usually suffice to distinguish the various disorders.

Early recognition of an arteriovenous fistula, and immediate surgical excision of the vascular defect will prevent the development of gradual and progressive cardiac deterioration; whereas, delay in recognition and treatment may produce only partial reversibility in heart size and hemodynamics of the central circulation. Reid[17] has said: "It is too true that we often fail to appraise properly chronic affections which, while life lasts, are no serious handicap to the individual. . . . It is in such a manner that most abnormal arteriovenous communications must be considered, for they are usually chronic affections, often worrying little, but often subtracting days from the end of one's life.'"

## Summary

Renal arteriovenous fistulas occur rarely; according to recent reviews only 17 cases have been previously reported. Two of the fistulas followed nephrectomy. Another postnephrectomy arteriovenous fistula is reported, which increases the totals to 18 and to 3 cases, respectively. The importance of a detailed history, a careful physical examination, and fluoroscopy of the chest is stressed as a reliable diagnostic approach in the recognition of an extracardiac shunt and its effect on the central circulation. Some clinical and diagnostic features are discussed and mention is made of other conditions that need to be considered in the differential diagnosis. The pathologic physiology of an arteriovenous fistula is briefly discussed. The importance is emphasized of recognizing abnormal cardiac findings secondary to a renal arteriovenous shunt which represents a curable form of heart disease after excision of the vascular defect.

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# RETINOPEXY OR LAMELLAR SCLERAL RESECTION FOR RETINAL DETACHMENT

## Analysis of Results in 126 Consecutive Cases*

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IN 1953, a five-year survey of the results of retinopexy for retinal detachment in 103 consecutive patients at Cleveland Clinic was reported.[1] It is the purpose of this paper to present a similar survey of the results of retinopexy and of lamellar scleral resection for retinal detachment in 126 consecutive patients treated here during the succeeding five-year period from 1953 through 1957.

In evaluating the results in the original and also in the current series, the same criterion of a cure as presented at the symposium on retinal detachment[2] was applied: complete reattachment of the retina for not less than six months postoperatively. However, as will be noted later, complete reattachment does not necessarily imply visual improvement.

### Preoperative Factors

During the five-year period from 1953 through 1957, 331 consecutive patients having retinal detachment were examined here, 11 of whom had bilateral detachment. Of the 331 patients, 126 came to surgery.

Symptoms in the 126 patients were characteristic of those generally reported: blurred vision (126 patients), light flashes (60 patients), subjective scotoma (33 patients), hemorrhage preceding detachment (4 patients), pain (1 patient), and metamorphopsia (1 patient).

The conditions associated with the detachments in the patients were: aphakia (22 patients); trauma (19 patients); glaucoma (6 patients); hypertension (5 patients); retinal detachment or aphakia in the opposite eye (4 patients each); basal-cell carcinoma or carcinoma of the rectum, or anterior and posterior uveitis (2 patients each); and abscessed teeth, arteriosclerotic heart disease, Bell's palsy, cancer of the uterus, cerebral thrombosis, cholelithiasis, corneal ulcer, Cushing's syndrome, dislocated lens, epididymitis, exotropia, glomerulonephritis, gout, Graves' disease, hemophilia, hypothyroidism, intermittent claudication, keratonus, malignant melanoma, pyelonephritis, subdural hematoma (1 patient each). Many factors are involved in the pathogenesis of detachments. All factors must be metic-

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ulously considered before treatment is recommended. If a tumor is suspected, a radioactive phosphorus ($P^{32}$) uptake study may be diagnostically helpful. Not all detachments are indications for surgery; for example, one patient who had toxemia of pregnancy recovered normal vision and fields after delivery, without ophthalmic surgery. However, as stated by Funder,[3] the prognosis for good vision in the unaffected eye appears to be poor, and thus every effort should be made to cure the detachment in the affected eye.

The preoperative factors in the first and in the current series are briefly compared in *Table 1.* In each series there were more men than women; the percentages

**Table 1.**—*Preoperative factors in two series of patients having retinal detachment*

| Preoperative factors | Number of patients | |
|---|---|---|
| | First series[1] of 103 patients (1948 through 1952) | Current series of 126 patients (1953 through 1957) |
| Sex | | |
| Male | 60 | 72 |
| Female | 43 | 54 |
| Duration of detachment | | |
| less than one month | 79 (76.7%) | 96 (76%) |
| Refractive error | | |
| Myopia | 17 | 9 |
| Hyperopia | 19 | 8 |
| Mixed astigmatism | | 7 |
| Compound hyperopic astigmatism | | 14 |
| Compound myopic astigmatism | | 34 |
| Age, years | | |
| 6 - 40 | | 19 |
| 40 - 70 | | 104 |
| 70 - 90 | | 3 |

of patients having retinal detachments less than one month were about equal in both series. The hyperopes and the myopes were about equal in number, yet the compound myopic astigmatism was more prevalent than the compound hyperopic astigmatism. One hundred and four patients (83 per cent) were in the age group of 40 to 70 years.

Billowy detachments (108 patients, 86 per cent) were more prevalent than flat detachments (18 patients, 14 per cent). Holes were found in 83 patients, 13 of which had disinsertions, 6 patients had two holes, and 3 patients had three holes. In these patients the detachment was complete in 10 eyes. It was inferior in 27, superior in 31, temporal in 48, and nasal in 1. Sixty-three (50 per cent) of these patients had holes in the superior quadrants.

Of the 126 patients who underwent surgery, 106 had three to six days of bed rest before the operation; only 15 patients had bed rest for less than three days, and 5 had more than six days. Preoperative bed rest is believed to be important for the following reasons: (1) the retina becomes flatter, facilitating localization of tears or holes; (2) in the elderly patients other diseases may be revealed that are better treated medically before than after operation.

## Results of Surgery

Of the 126 patients, 77 patients underwent retinopexy and 49 lamellar scleral resection. Two of the resections were buckling procedures that involved implantation of polyethylene tubes. The results in these operations are compared with those presented in the previous survey *(Table 2)*.

In the current series the cure rate of 51 per cent in the 77 patients who underwent retinopexy was better than that in the previous series of 49 patients (47.5 per cent were cured). Likewise, the cure rate in patients who underwent lamellar scleral resection was 51 per cent in 49 cases. In the present series the billowy detachments with holes responded to surgery better than did those without holes. The flat detachments with holes responded better to surgery for retinal detachment than did the ones without holes.

Sixteen of the 126 patients had no follow-up and for statistical purposes were considered failures. If these cases were deleted then the over-all cure rate for a primary procedure would be 58 per cent.

In analyzing the successes, we note that some of the patients recovered visual fields and visual acuity, while others achieved reattachment with recovery of visual acuity or recovery of visual fields but not both. The results confirm the previous statement that complete reattachment does not necessarily mean visual improvement.

Of the 126 patients, 16 had recurrence of retinal detachment which required reoperations. One patient had two reoperations. Lamellar scleral resection was performed in nine recurrences with improvement in five cases (55 per cent). Retinopexies were performed in eight recurrences with improvement in three cases (38 per cent). From these percentages it would appear that lamellar scleral resection is better as a secondary operation than is retinopexy.

In the 22 aphakic eyes of the 126 patients, 14 lamellar scleral resections were performed with improvement in 6 (43 per cent). Nine retinopexies were performed

on aphakic eyes with improvement in three (33 per cent). Again, lamellar scleral resections gave the best results.

### Postoperative Complications

All of the 126 patients were kept bedfast and supine for 7 to 14 days postoperatively. In all of the patients, conjunctivitis or some other conjunctival reaction occurred postoperatively; however, only one patient had a severe blepharitis. Exotropia was present in seven patients; complicated cataract was present in nine. Other complications were pulmonary embolus (one patient), pulmonary infection (one patient), keratitis (two patients), urinary retention (one patient). One malignant melanoma was found on subsequent enucleation.

**Table 2.**—*Results of surgery for retinal detachment in two consecutive series of patients*

| Factors | Number of Patients | | | |
|---|---|---|---|---|
| | First series[1] (1948-1952) | | Current series (1953-1957) | |
| | Cured, no. of patients (percentage of total) | Total no. of patients | Cured, no. of patients (percentage of total) | Total no. of patients |
| Type of operation | | | | |
| Retinopexy | 49 (47.5%) | 103 | 39 (51%) | 77 |
| Lamellar scleral resection | — | — | 25 (51%) | 49 |
| Total | 49 (47.5%) | 103 | 64 (51%) | 126 |
| Type of detachment | | | | |
| Billowy | | | | |
| With holes | 10 (35.7%) | 28 | 40 (53.3%) | 75 |
| Without holes | 28 (55%) | 51 | 13 (39.3%) | 33 |
| Total | 38 (48.1%) | 79 | 53 (49%) | 108 |
| Flat | | | | |
| With holes | 4 (100%) | 4 | 6 (75%) | 8 |
| Without holes | 7 (35%) | 20 | 5 (50%) | 10 |
| Total | 11 (46%) | 24 | 11 (61.1%) | 18 |

## Comment

Our cure rate of 51 per cent is based on an over-all series including primary and secondary procedures. Colyear and Pischel[4] reported a 75 per cent cure rate in 440 cases. They state that the causes of failure in surgery for retinal detachment stem from failure of early recognition, failure to find and to close the primary tears, and failure to close satellite tears. They believe that the majority of cases can be cured by diathermy alone, and that scleral shortening procedures should be reserved for eyes with retinal shrinkage or vitreous adhesion, aphakic eyes with retinal detachment occurring soon after cataract surgery, and for certain cases of severe myopia, multiple tears, and large disinsertions. Our experience leads us toward that trend of thought.

## Summary

Of 331 consecutive patients having retinal detachment examined during a five-year period (1953 through 1957), 126 were operated upon; 77 of these patients underwent retinopexy, and 49 lamellar scleral resection. Pathogenic factors associated with the detachments should be considered in each case, because a certain proportion of patients having retinal detachments are not good candidates for surgery for other reasons, but rather should be treated medically. Localization of holes is of primary importance. To this end, preoperative bed rest is believed to be of great assistance in stabilizing the retina to facilitate examination. The possibility of the presence of a malignant melanoma must always be considered. In cases of suspected tumor, radioactive phosphorus ($P^{32}$) studies may be helpful.

Comparable results between retinopexies and lamellar scleral resections are shown. Surgery should not be limited to one procedure, but the surgeon should evaluate each case and use the appropriate procedure.

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# ANATOMIC FEATURES COMMON TO THE ARNOLD-CHIARI AND THE DANDY-WALKER MALFORMATIONS SUGGEST A COMMON ORIGIN

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. . . . in every . . . . art, fundamental matters are perennially being discovered, discredited, forgotten, rediscovered and reaffirmed . . . .

John Homans[1]

MILD examples of the Arnold-Chiari and Dandy-Walker malformations were described in adults by Chiari,[2,3] by Walker,[4] as well as by subsequent authors. Gardner, Abdullah, and McCormack[5] have shown that the mild examples of these two malformations found in adults have so many anatomic features in common that they must arise from a common cause, namely, embryonal atresia of the fourth ventricle. The purpose of this communication is to point out that the same is true of the severe forms encountered in the hydrocephalic infant.

## Definition of Terms

Chiari,[2] in 1891, described in detail three degrees of a deformity of the hindbrain that he attributed to hydrocephalus of the forebrain. This description appeared three years prior to Arnold's[6] incidental and quite incomplete account of the same deformity. Chiari's type 1 deformity, now usually referred to as a "pressure cone," consisted essentially of a herniation of the cerebellar tonsils through the foramen magnum. His type 2, subsequently entitled the "Arnold-Chiari malformation" by Arnold's students,[7] consisted of a herniation of the inferior vermis, pons, medulla, and the compressed fourth ventricle through the foramen magnum with a steplike formation of the medulla and a shortening of the cervical cord. In his type 3, the cerebellum was herniated into a high cervical meningocele. In his commonly quoted second paper, Chiari[3] reported 14 cases of type 1, all in adults or adolescents, only one of whom had myelomeningocele, and seven cases of type 2, all in infants with myelomeningocele. He pointed out that both types were caused by hydrocephalus and that type 2 was merely a severe form of type 1. Some authors since Chiari have denied that his type 1 (pressure coning) is related to his type 2 (Arnold-Chiari malformation) and, in the latter condition, have substituted cause for effect by attributing the hydrocephalus to the malformation.

It is unfortunate that the term "Arnold-Chiari malformation" has become so firmly established, because this term confuses the issue by referring only to Chiari's type 2 and thus tends to set it apart from Chiari's type 1. My observations support

Chiari's convictions that type 1 is a mild form of type 2 and that both are the result of hydrocephalus, and I therefore shall revert to Chiari's terminology.

The term "Dandy-Walker syndrome" was introduced by Benda[8] to describe a different deformity of the hindbrain in which, instead of compression, there is dilatation of the fourth ventricle. This deformity, also caused by hydrocephalus, was attributed by Dandy[9] to congenital occlusion of the foramens of Magendie and Luschka. This occlusion subsequently was shown by Taggart and Walker[10] to result from lack of perforation of the embryonic rhombic roof. In this malformation, as in Chiari's, severe forms usually are discovered in infants and mild forms in adolescents or adults. In the Dandy-Walker deformity the posterior attachment of the tentorium is higher than normal, and the hydrocephalus, therefore, affects the hindbrain more than the forebrain *(Figs. 1-3)*. In the Arnold-Chiari malformation, hereinafter referred to as the Chiari type-2 malformation, the attachment of the tentorium is lower than normal and, since this is accompanied by compression of the hindbrain and frequently also of the midbrain, the hydrocephalus can affect only the forebrain *(Fig. 4)*.

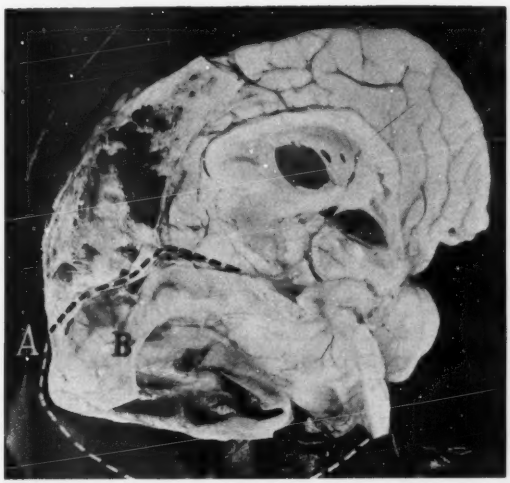



**Fig. 1.** Dandy-Walker malformation in a hydrocephalic infant seven and one-half months old. The sagittally sectioned forebrain and hindbrain have been reassembled. The dotted line represents the approximate limits of the enormously distended posterior fossa. The junction of the sagittal and lateral sinuses is at A. The membrane seen to the left of the attenuated cerebellum is the left leaf of the diaphragm. It includes the falx cerebelli B and is lined by the transparent roof of this enormous fourth ventricle. Note also the flattening of the brain stem. This specimen was hardened in situ by embalming the body and injecting concentrated formalin into the ventricles six hours prior to necropsy.

**Fig. 2.** Dandy-Walker malformation, the same case as that of *Figure 1*. Posterior aspect of the brain before removal from the skull. The great depth of the cavity is not apparent in this photograph. The junction of the sagittal with the lateral sinuses above the level of the lambdoid sutures forms a Y rather than a T. The tentorium, the small cerebellar lobes and the attenuated vermis are dislocated cephalad. The brain stem is flattened, widened, and elongated so that the floor of the fourth ventricle extends through the foramen magnum. In most of the reported cases only the membranous roof has been herniated through the foramen. The jugular foramens stand out prominently. Above and lateral to them may be seen strands of choroid plexus.

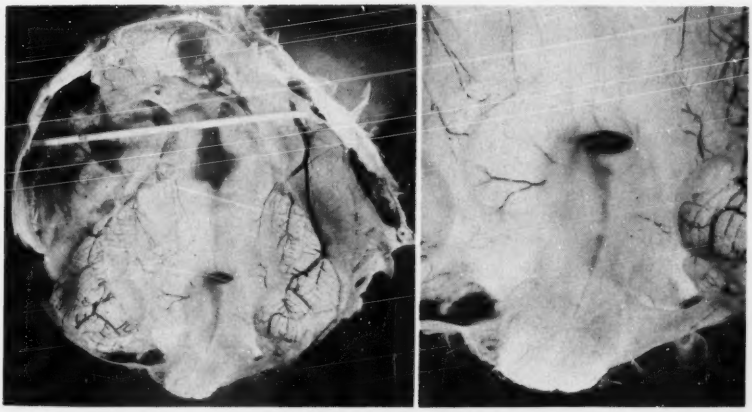
## Anatomic Features

It is a medical axiom that to develop a proper concept of the nature of a disease process, one should begin with a study of mild cases. Anatomic features shared by the mild (usually adult) cases of Chiari and Dandy-Walker malformations are as follows:[5] compensated hydrocephalus, either communicating or noncommunicating; hydromyelia (dilatation of the central canal); syringomyelia (syrinx or diverticulum communicating with the central canal); basilar impression; scoliosis; thickening of the meninges at the level of the foramen magnum; and closure of the foramens of the fourth ventricle by membranes that represent persisting portions of the embryonic rhombic roof.

Anatomic features common to the severe (usually infantile) forms of these two malformations will be shown to be as follows: uncompensated hydrocephalus, either communicating or noncommunicating; hydromyelia; syringomyelia, myelomeningocele; encephalocele; thickening of the meninges at the level of the foramen magnum; dislocation of the caudal portion of the fourth ventricle into the spinal canal and closure of the foramens of the fourth ventricle by membranes that represent persisting portions of the embryonic rhombic roof.

*Hydrocephalus.* The progressive enlargement of the head which occurs in most infants with the Chiari type-2 malformation, indicates that the hydrocephalus is uncompensated. Russell and Donald[11] showed that this hydrocephalus may be either communicating or noncommunicating.

In the Dandy-Walker malformation of infancy, the accompanying hydrocephalus also is uncompensated. In three cases described by Benda,[8] necropsy disclosed that one was noncommunicating and two were communicating. In four cases reported by Schreiber and Reye,[12] antemortem tests indicated that the hydrocephalus was noncommunicating in one and communicating in three. In Matson's[13] surgical experience with eight cases of this condition, opening the occluded fourth ventricle relieved the hydrocephalus in three cases but in the



A B

Fig. 3. Dandy-Walker malformation, the same case as that of *Figures 1* and *2*. A, The hindbrain and attached tentorium have been removed and floated in water. One can see the torn edge of the delicate membrane (rhombic roof) that previously had formed an invisible lining of the entire inner surface of the dura and the tentorium and had herniated through the foramen magnum. It is attached to the taenia and to the cerebellum at its line of contact with the dura and the tentorium. On either side of the transected medulla, a tiny outpouching of the delicate membrane may be seen which had herniated into the jugular foramens. B, These are better shown in the enlargement. Similar outpouchings into the acoustic meatuses apparently had been divided along with the eighth cranial nerves.

remaining five it served merely to "convert" the noncommunicating hydrocephalus into the communicating variety. Therefore, in the Dandy-Walker as in the Chiari type-2 malformation, the uncompensated hydrocephalus may be either communicating or noncommunicating, or a combination of both, with inadequate absorptive capacity of the subarachnoid space superimposed upon partial ventricular obstruction. Ventricular obstruction in no case can be really complete because all living tissues, including the walls of the ventricles, are permeable to water in some degree.

*Hydromyelia and syringomyelia.* The infant with a Chiari type-2 malformation usually has hydromyelic dilatation of the central canal of the cord. This relationship, first described by Chiari,[2,3] was demonstrated by Ingraham and Scott[14] in 8 of 20

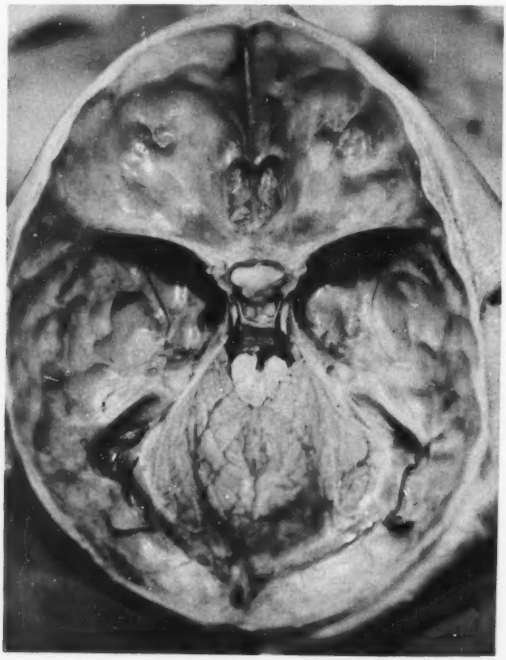


**Fig. 4.** A case of Chiari type-2 malformation in a child aged four years and five months with congenital hydrocephalus and myelomeningocele. The same method of fixation was employed as described in *Figure 1.* The hydrocephalic forebrain has been removed. The entire attachment of the tentorium is dislocated caudally including the superior petrosal sinuses which are depressed well below the petrous ridges. Note that the cerebral peduncles are displaced downward behind the clivus into the posterior fossa while the superior surface of the vermis bulges upward through the incisura. The aqueduct, compressed in the midbrain hernia, is not visualized. This necropsy study illustrates the advantages of fixation in situ and removal of the hydrocephalic cerebral hemispheres before disturbing the relationship of the structures of the posterior fossa.

cases, and by Cameron[15] in 20 of 22 cases. An infant with this malformation, also may have a true syrinx or cavitation paralleling the dilated central canal of the cord as was described by Lichtenstein[16] *(Fig. 5)* and by Cameron.[15]

Benda[8] found the combination of hydromyelia and syringomyelia also in the infant with Dandy-Walker malformation. In his case 3 he described "congenital syringomyelia of the hydromyelic type" throughout the entire length of the spinal cord. The gray matter of the cord had failed to differentiate in the normal way, and the central canal formed a large slit walled by ependymal cells. At some levels the cavity was enlarged and filled with spinal fluid while at others a secondary cavity was formed within the gray matter. In his case 4B the gray matter of the cord "was completely undifferentiated, forming a central syringomyelia." Thus it is apparent that the infantile forms of the Dandy-Walker and of the Chiari malformations may be accompanied by hydromyelia and a syrinx as well.

Inasmuch as the ventricles and the central canal of the cord constitute a single cavity, the term "hydrocephalomyelia" has been proposed for the state in which both are dilated.[17]

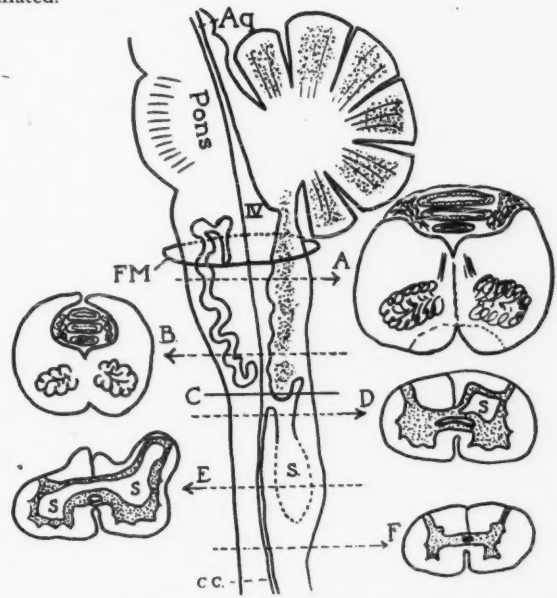



**Fig. 5.** Schematic drawing of a midsagittal section through the hindbrain and upper cervical cord of an infant with hydrocephalus, Arnold-Chiari malformation, and myelomeningocele. FM indicates the foramen magnum, S the syrinx, cc. the central canal, and C the level of transection at necropsy. (Courtesy of Lichtenstein, B. W.: Arch. Neurol. & Psychiat. 49: 881-894, p. 890, June 1943; A.M.A. Arch. Neurol. & Psychiat.) Note the lack of perforation of the rhombic roof (embryonal atresia of the fourth ventricle).

*Myelomeningocele.* The association of the Chiari type-2 malformation with myelomeningocele described by Chiari,[2] recently has been restudied by Cameron[15] who, in 26 infants with myelomeningocele, found the Chiari type-2 malformation in its typical form in 22, "atypical variants" of it in two (one of these was Chiari's type 1), and no malformation in the other two.

It is not generally recognized that an infant with Dandy-Walker malformation also may have myelomeningocele. Dandy[9] shows a photograph of such a patient, and Benda[8] describes a myelomeningocele in his case 3 referred to above. Myelomeningocele, therefore, is still another feature associated with the severe Dandy-Walker as well as with the Chiari type-2 malformation.

*Encephalocele.* My survey of the literature to date has disclosed no fully documented cases of encephalocele associated with Chiari type-2 malformation unless it be those of Cameron.[15] In this author's[15] 26 cases of "spina bifida" in infants, there were two cases in which there was coexisting "cranium bifidum." The roentgenogram of one case showed a large encephalocele and severe craniolacunia. This latter condition Cameron[15] found only in severe cases of Chiari type-2 malformation, so the reader must assume that this patient had both encephalocele and Chiari type-2 malformation although the author does not specifically so state.

The association of encephalocele with the Dandy-Walker malformation, on the other hand, is well documented. Bland Sutton[18] in 1887, described and illustrated a case in which the cerebellum was "virtually absent" and a large encephalocele containing choroid plexus protruded from a bulging posterior fossa. Dandy[19] also showed an illustration of an encephalocele protruding through a hiatus in the occipital bone, communicating with a greatly distended fourth ventricle, and "participating in the hydrocephalus caused by a block of the foramen of Magendie" *(Fig. 6).* Schreiber and Reye[12] described two cases of occipital encephalocele communicating with a Dandy-Walker malformation of the posterior fossa. Encephalocele, therefore, is encountered in the infant with the Dandy-Walker and perhaps also with the Chiari type-2 malformation.

*Membranes closing the foramens of the fourth ventricle.* Taggart and Walker[10] described closure of the enlarged foramens of the fourth ventricle by persisting portions of the membranous rhombic roof as the cause of their "congenital atresia of the foramens of Magendie and Luschka" (Benda's[8] Dandy-Walker syndrome). Subsequent authors, with one exception (Benda[8]), have accepted this explanation. Histologically similar though less expanded membranes occluding the foramens of Magendie and Luschka may be readily demonstrable in the Chiari type-1 malformation. Russell's[20] case 19 is an example *(Fig. 7).* In this infant, whose spinal cord was tethered at the level of a lumbosacral meningocele, she described the brain as follows: "There was gross internal hydrocephalus, involving all ventricles; the aqueduct measured 0.5 cm. in diameter. At the foramen magnum the medulla was closely enveloped by a cone-shaped mass of cerebellar tissue . . . which proved,

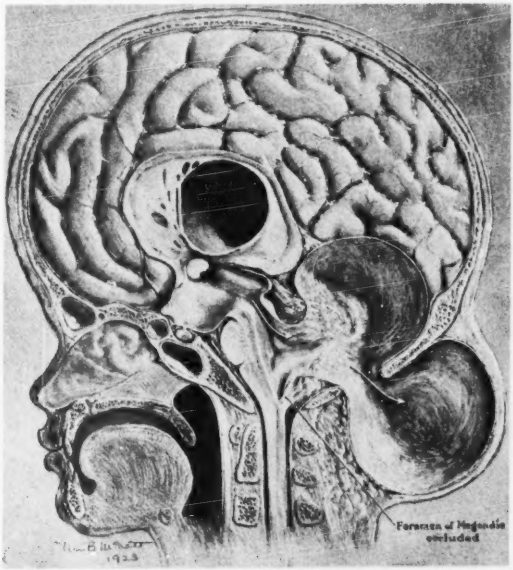



Fig. 6. Dandy-Walker malformation with encephalocele. (Courtesy of W. E. Prior Co., Inc.; Dandy, W. E.: The Brain. *In* Lewis, D. D.:: *Practice of Surgery,* 1932, p. 258.

on dissection, to be composed of the tonsils. When separated, a translucent membrane was found at the site of the foramen of Magendie ... There was great ballooning of the tissue at the foramina of Luschka, forming a translucent bleb, about 1 cm. in diameter, on either side ... In a mid-sagittal section the membrane occluding the foramen of Magendie is composed, above and below, of fibrillary neuroglia lined, towards the ventricle, with a layer of ependymal cells. The central third of the structure is occupied by a flattened mass of choroid plexus. Externally the membrane is coated with the pia, which is reflected on to its surface from the adjacent cerebellum and medulla oblongata." Russell,[20] in this case, is describing a Chiari type-1 malformation in association with what many authorities would consider an abortive myelomeningocele. Chiari,[3] and Cameron[15] as well, has described myelomeningocele in association with a Chiari type-1 malformation. Russell's[20] histologic description of this membrane occluding the foramen of Magendie corresponds closely with that of her case 15 which she considered a probable example of the Dandy-Walker malformation.

Dandy may have been the first to recognize that the Chiari type-2 malformation is the result of obstruction of the foramens of Magendie and Luschka. In a paper[9] on hydrocephalus due to occlusion of these foramens, he includes the following case: "In a fourth case, a dorsal meningocele was present at birth and

Fig. 7. Membrane obstructing the foramen of Magendie in an infant with a Chiari type-1 malformation, a lumbosacral meningocele, and a tethered cord. Each foramen of Luschka also was closed by a bulging membrane in this case. (Courtesy of Russell, D. S.: M. Res. Council Special Rep. Ser. No. 265, p. 34; H. M. Stationery Office, 1949; the Controller, H. M. Stationery Office, 1959.)

hydrocephalus was observed 2 months after birth. A dense scar covered the foramen of Magendie and the contiguous region. The cerebellum was firmly bound to the medulla and pons, there being no bulging fourth ventricle between. A large cerebellar hernia projected into the spinal canal. The pia-arachnoid was adherent to the dura over most of the area exposed at operation." Dandy recognized, despite the lack of dilatation of the fourth ventricle in this case, that obstruction of the foramens of Magendie and Luschka was the cause of the hydrocephalus and of the hernia of the hindbrain. He attributed the associated thickening and adhesions of the leptomeninges to inflammation. Others have reached a similar conclusion even in cases where microscopic study has revealed the presence of neuroglial elements and little or no evidence of inflammation. In the Chiari type-2 malformations the foramens of Luschka are so compressed in the spinal canal that they are almost impossible to study, but a membrane occluding the foramen of Magendie may be demonstrated in some cases *(Figs. 8* and *9).*

Thus, it is apparent that in the Chiari type-1 and type-2 malformations, as in the mild and the severe Dandy-Walker malformations, the foramens of the fourth ventricle may be occluded by membranes* that, in view of their attachments, obviously represent persisting portions of the embryonic rhombic roof. That these delicate membranes are not always found is not surprising in view of the

*Not yet proved for the foramens of Luschka in the Chiari type-2 malformation.

**Fig. 8.** Chiari type-2 malformation in an infant. (Courtesy of Moncrieff, A., and Norman, R. M.: Greenfield, J. G.: *Neuropathology:* Edward Arnold (Publishers) Ltd., 1958, p. 314.) The attachment of the bulging membrane to the cerebellar hernia and the brain stem indicates that it is the rhombic roof. Compare with *Figures 5, 7,* and *9.*

severe stresses imposed upon them by the squeezing of the aftercoming hydrocephalic head in its passage through the birth canal.

Thickening and fusion of the leptomeninges at the level of the foramen magnum often is present in the Chiari type-1 and type-2 malformations. It has also been described in both the mild and the severe forms of the Dandy-Walker malformation, as in case 1 of Gardner, Abdullah, and McCormack[5] and in case 1 of Taggart and Walker.[10]

The occluded lower end of the fourth ventricle is herniated through the foramen magnum both in the severe Dandy-Walker *(Fig. 2)* and the Chiari type-2 malformations *(Figs. 5, 8,* and *9).*

## Discussion

The neural tube of the embryo is a closed cavity consisting of the primitive ventricles and the central canal of the cord. Its lumen is large compared to the thickness of its walls, a relationship which in later life constitutes hydrocephalus and hydromyelia (hydrocephalomyelia). This disproportion of lumen to neural tissue, is a feature of normal embryonal development and, as shown in Weed's[21]

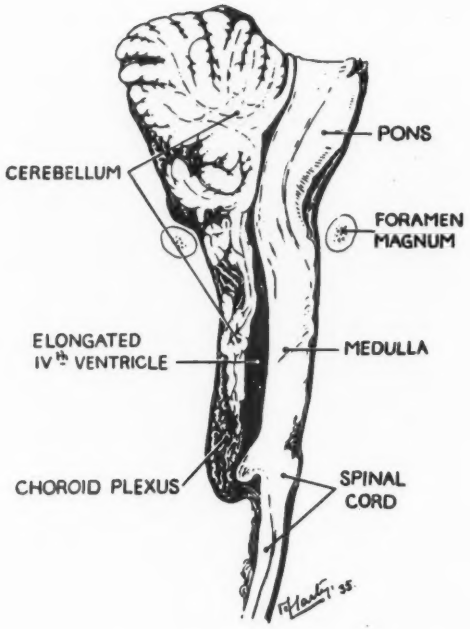



**Fig. 9.** Chiari type-2 malformation. (Courtesy of Russell, D. S.: M. Res. Council Special Rep. Ser. No. 265; H. H. Stationery Office, 1949, p. 23; the Controller, H. M. Stationery Office, 1959.) As in *Figure 8*, the cerebellar hernia appears to have pulled the attached brain stem down with it as evidenced by the posterior eversion of the obex and the resultant kinking of the upper end of the central canal.

illustrations, it reaches its most advanced degree shortly after the choroid plexus begins to elaborate fluid. At this stage the distended head of the embryo is a thin-walled, almost transparent cyst *(Fig. 10)*. The normal embryo recovers from this "physiologic hydrocephalus" as it becomes compensated by the increasing permeability of the rhombic roof and of the absorbing areas in the subarachnoid space.

Weed[21] believed that, if the rhombic roof were not sufficiently permeable at this critical period, the retained fluid would overdistend the lumen of the neural tube. In this case it would not filter through the roof in a quantity sufficient to accomplish adequately the job of dissecting open the developing subarachnoid spaces; that if this happened, the obstructive hydrocephalus would result in communicating hydrocephalus. This significant observation made in 1917 has been largely forgotten in present-day attempts to explain the origin of congenital hydrocephalus.

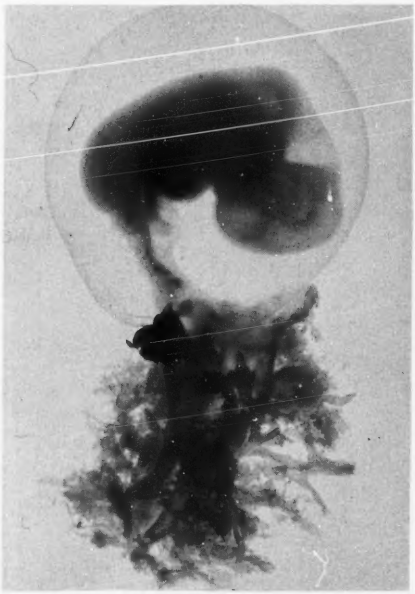


Fig. 10. At six weeks, when the choroid plexus begins to function,[21] the head of the human embryo is a thin-walled bag of water. The most translucent area is the rhombic roof. This specimen was photographed after it had been made relatively opaque by formalin fixation.

The pulsating choroid plexus, a relatively enormous structure in the embryo acts like an unvalved pump to generate a pulse wave in the ventricular fluid.[22] As long as the rhombic roof does not perforate, this pulse wave is funneled into the relatively large central canal. After the roof perforates to form the foramens, the ventricular fluid pulse wave is shunted into the spinal subarachnoid space. Thereafter the bypassed central canal, containing no choroid plexus and subjected to this pulsating pressure on its outer surface, narrows and becomes a vestigial structure. However, it will dilate again, in the experimental animal, if the foramens of the fourth ventricle are occluded by the reaction resulting from the intracisternal injection of kaolin.[23]

Hydrocephalomyelia is present prior to the opening of the foramens of the fourth ventricle in the normal embryo; it is also present in the infant with Chiari type-2 malformation, and in the infant with Dandy-Walker malformation.* This implies that in these newborn infants, this state, which is normal only in the embryo, has been preserved because of a failure of the foramens of the fourth ventricle to open (embryonal atresia). The anatomic attachment and the microscopic appearance

*Hydrocephalomyelia also is present in the cases of mild Chiari and Dandy-Walker malformations in adults.[5,24]

of the membranes that enclose the foramens in these malformations support this concept.

The hydrodynamic stresses responsible for these malformations may be compared to the stresses existing when the inflating pressure in an automobile inner tube exceeds the elastic resistance of the weakest portion of its wall; as this occurs, and despite the fact that the pressures in all parts of the tube are identical, a localized bulging and attenuation develops *with a consequent pushing away of the surrounding zone.* Transferred to the embryo with inadequate permeability of the rhombic roof, this phenomenon may affect the covering of either the hindbrain or the forebrain. If, in a given case, the covering of the hindbrain happens to offer less resistance, it will expand disproportionately and push the tentorium and the forebrain in a cephalad direction (Dandy-Walker malformation). On the other hand, if the covering of the forebrain happens to be more yielding, it will expand and displace the tentorium and the compressed hindbrain in a caudad direction (Chiari type-2 malformation). In the latter case the herniation of the hindbrain structures through the foramen magnum will meet relatively little resistance from the immature dentate ligaments. The herniation will be exaggerated in those cases in which the caudal portion of the neural tube is open (myelomeningocele).

If the permeability of the rhombic roof is only mildly or temporarily impaired, there may be little dislocation of the tentorium and the hydrocephalus may result in a mild Dandy-Walker or in a Chiari type-1 malformation. Such a mild degree of embryonal hydrocephalus may become compensated so early in intrauterine life that the ventricles are restored to normal size by the time of birth. However, in these cases, the central canal may maintain its patency as an offshoot of the closed ventricular system. The pulsations of the ventricular fluid then are funneled into it throughout life, and slowly progressing dilatation of the central canal may result in the clinical picture of syringomyelia.[5] In the Chiari type-2 malformation, the upper end of the central canal may be doubled back on itself and closed off in the posterior buckling of the medulla *(Figs. 8* and *9).* This buckling is due to the fact that the rhombic roof is more free to move caudally than is the floor which must push the cervical cord ahead of itself.

The neurologic surgeon is accustomed to the concept that dilatation occurs uniformly in all portions of the ventricular system anterior to a point of obstruction.* This concept has made it reasonable for him to believe that the Dandy-Walker and Chiari type-1 malformations are due to obstruction of the outlets of the fourth ventricle.† However, this same concept has obscured his thinking in regard to the

**This concept applies to the brain in the nonexpansible skull where the ventricular dilatation is due to uniform compression of brain tissue; it does not apply to the brain within the soft, immature skull in which one part will expand more than another with resulting unequal stretching and attenuation of the underlying brain.*

†*The exaggerated dilatation of the fourth ventricle in the Dandy-Walker syndrome cannot be the result of a higher pressure in this ventricle since it communicates freely with the other ventricles. The unequal dilatation, therefore, can be explained only on the basis of a difference in the yielding qualities of the coverings.*

Chiari type-2 malformation in which the downward displacement of the tentorium has compressed and narrowed the lumen not only of the hindbrain (fourth ventricle) but also, in some instances, the lumen of the midbrain with resulting stenosis and forking (due to longitudinal wrinkling of the wall) of the aqueduct. Furthermore, the stretching of the midline structures in the sagittal plane, which results from the increasing *sagittal diameter* of the expanding skull, may cause an approximation of the lateral walls of the third ventricle with thickening (Cameron[15]) rather than attenuation of the massa intermedia *(Fig. 11)*. This stretching of the midline structures in the sagittal plane also may be responsible for attenuation of the falx (Cameron[15]), for fenestration of the septum pellucidum, and for dilation of the foramens of Monro.

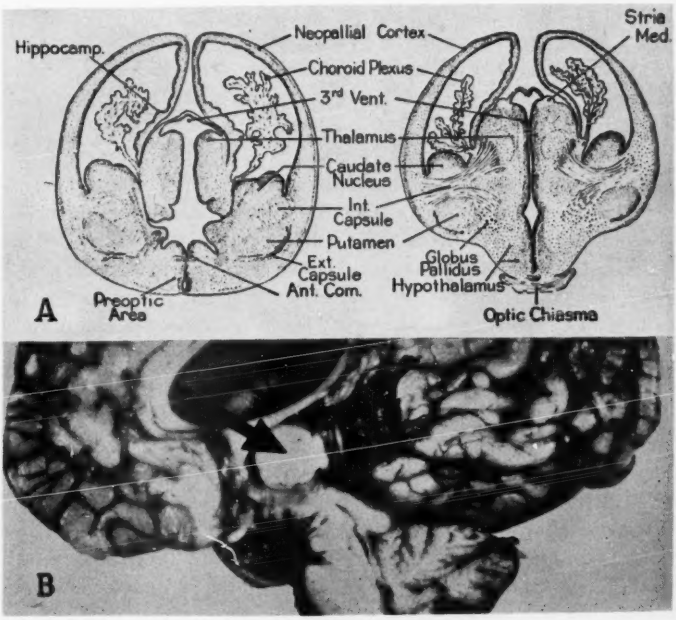



**Fig. 11.** A, Coronal sections of the brain of a three-month-old fetus. (Courtesy of Patten, B. M.: *Human Embryology*, Ed. 2; modified after Kodama; McGraw-Hill Book Co., Inc., 1953, p. 353.) It is apparent at this stage that ballooning of the membranous skull would result in stretching of the structures in the sagittal plane, which would result in closer approximation of the thalami and widening of their area of contact, i. e., of the massa intermedia. B, Brain of an infant with Chiari type-2 malformation. The arrow points to the interthalamic ramus, greatly thickened by approximation of the thalami.[15] (Courtesy of Cameron, A. H.: J. Path. & Bact. 73: 195-211, Jan. 1957.) Note also the deformity of the quadrigeminal plate ascribed by Feigin[28] to developmental arrest, but more likely the result of downward dislocation and compression of the midbrain.

It is planned, in a future communication, to "rediscover," and perhaps to "reaffirm," Morgagni's[25] belief, which was later "discredited" by Von Recklinghausen[26] and has since been all but "forgotten," that myelomeningocele results from the disruption of a neural tube that has closed rather than from a failure of the tube to close.

## Conclusions

The several anatomic features common to the Chiari type-2 and to the Dandy-Walker malformations suggest: that these deformities must have a common cause; that Chiari's hindbrain malformation is the result of hydrocephalus as he[2] stated in 1891, and not the cause of it as was advocated by Russell and Donald[11] in 1935, nor is the deformity produced by traction of the tethered cord as suggested by Penfield and Coburn[27] in 1938; that Chiari's type-1 malformation (pressure coning) is, as he[2,3] stated, a mild form of his type-2 (Arnold-Chiari) malformation; that, as proposed by Weed[21] in 1917, inadequate permeability of the embryonic rhombic roof may cause congenital hydrocephalus, both obstructive and communicating; that the Chiari type-2 and Dandy-Walker malformations with their accompanying hydrocephalomyelia are due to embryonal atresia of the fourth ventricle; that a normal hindbrain results if in embryonic life the rhombic roof differentiates properly and opportunely so that it is adequately permeable when the choroid plexus begins to function; that if the roof becomes adequately permeable a bit later than it normally should a Chiari type-1 or mild Dandy-Walker malformation may result; that if it becomes adequately permeable much too late or not at all a Chiari type-2 or a severe Dandy-Walker malformation may result.

## Acknowledgment

I should like to acknowledge my indebtedness and, at the same time, to extend my apologies to Dr. Dorothy S. Russell, to Dr. B. W. Lichtenstein and to Dr. Clemens Benda for making such free use of their material, and to Dr. A. H. Cameron, whose careful, painstaking study of 26 cases of spina bifida disclosed hitherto-undescribed anomalies associated with the Chiari type-2 malformation and which also stressed the frequency of other significant features that have led me to differ with him regarding the nature of the hydrodynamic stresses that cause them.

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# MOCK CIRCULATION TO TEST PUMPS DESIGNED FOR PERMANENT REPLACEMENT OF DAMAGED HEARTS

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IN the future it may become feasible to replace an irreparably damaged heart with a permanently indwelling mechanical pump to propel the blood through both the pulmonary and the systemic circulation. Setting aside for the moment the problems concerning clotting and injury to the blood cells or plasma, such a pump requires the mechanical definition as follows.

1. It should be a small double pump (right heart, left heart).
2. The pumping rate should be variable between 60 and 160 strokes per minute.
3. The output volume should be variable between 1.5 and no less than 5 liters per minute for each side of the pump.
4. The input pressure or 'atrial' pressure should be no more than 16 mm. of Hg, and no less than 0. In other words, suction should not be strong when available blood is not sufficient to fill the heart.
5. The output pressure of the right 'ventricle' should be 20 but capable of increasing to 80 mm. of Hg. The output pressure of the left 'ventricle' should be 120 but capable of increasing to 180 mm. of Hg.
6. The 24-hour output of the left side must equal that of the right side: the filling of each 'atrium' must determine the output of the corresponding 'ventricle.'
7. It is not absolutely necessary that the 'atria' contract, but the diastole should be sufficiently long to allow filling of the 'ventricles.' Wiggers [1] gives an example of diastole both in man and in dogs of 0.53 sec.; systole occurs in 0.27 sec.; and the time of maximal ejection to the ventricle takes only 0.09 sec. or 0.12 sec.
8. Possible source of energy: (a) a battery with a charger for direct-current motors or solenoids; or (b) an alternating power supply for motors operating on alternating current. The power supplies, (a) and (b), will be outside the body and will require wires into the chest; or (c), a small atomic power plant placed inside the chest.
9. Dissipation of the heat generated: the heat will be best transmitted to the blood so that the body and the lungs act as radiators.
10. The mechanical heart should be easy to insert, require no maintenance and should be easy to replace.

In order to reduce animal experimentation to a minimum, a simple system of mock circulation has been erected in which most of the tests can be performed *(Fig. 1)*. In the diagram the left and right 'ventricles' are separated to make it easier to outline the path of circulation, whereas in reality they are adjacent. The blood leaves the left 'ventricle' (LV) through a corrugated 'aorta' (AO) to enter

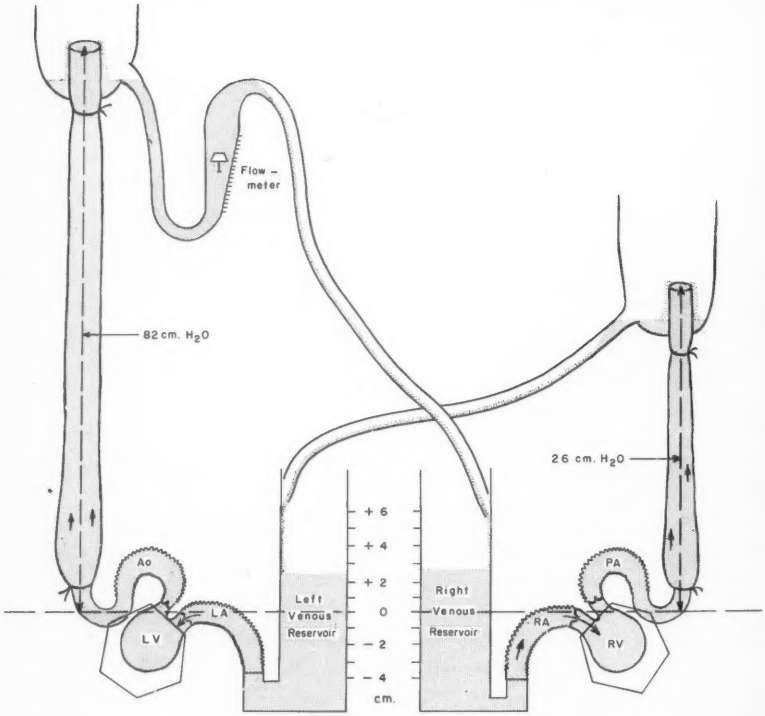


**Fig. 1.** Diagram of system for mock circulation. LV is the left 'ventricle'; RV is the right 'ventricle.' The 'ventricles' though actually adjacent are separated from each other in the diagram for clarity.

a distensible tube. The diastolic pressure in the base of the 'aorta' is determined by the height of the column of water of 82 cm., which corresponds to 60 mm. of Hg. One disadvantage of a fluid column is that inertia must be overcome to move a considerable amount of fluid in order to make room for the 'ventricular' output. This inertia is somewhat overcome by using distensible tubing or by surrounding its lowest part with an air chamber (not indicated in the diagram) under pressure.

The diastolic pressure can be varied by changing the height of the fluid column. Screw clamps or partial occlusions are not used to increase the resistance in a flow system, since their resistance increases with increased flow. The height of a fluid column does not change with a varying flow, and the resistance provided by it varies little. The overflow of the fluid column must be open to the air to avoid

formation of a siphon. From the overflow the fluid drains through a simple flowmeter* into the right venous reservoir, the level of which indicates the pressure in the right 'atrium' (RA). Blood from the right 'atrium' goes to the right 'ventricle' (RV), to the 'pulmonary artery' (PA) and then through another distensible tube. The height of this tube is only 26 cm., corresponding to approximately 20 mm. of Hg. Fluid from the right overflow is routed back to the left venous reservoir; the fluid level in the left venous reservoir indicates the pressure in the left 'atrium.' From there the fluid goes to the left 'ventricle' and the circulation is completed.

If the descending tubes are crossed over from left to right as in the diagram, the output of left and right 'ventricles' can be compared. In properly designed mechanical artificial hearts, an equilibrium is produced which stabilizes the left and right venous pressures at certain levels. If equilibrium exists, the flow rates on the right and the left sides must necessarily be the same, and a single flowmeter will serve both sides.

With this simple system of mock circulation we have been able to evaluate roughly the properties of several models of artificial hearts.[2] The solenoid heart†[3] proved to have too much suction; this was remedied by removing certain springs. A pendulum type of artificial heart seemed to fulfill the criteria postulated at the beginning of this paper, and subsequently proved satisfactory in an animal experiment. A roller type of artificial heart was satisfactory; a fourth type of artificial heart‡ is currently being tested.

The same equipment, minus the flowmeter, can be used for in vitro tests for hemolysis[4] if certain precautionary measures are taken to prevent formation of foam and froth in the overflow or descending lines. If the crossing over is eliminated and each descending line is returned to its own venous reservoir, the degrees of hemolysis in the left and the right sides can be compared.

## Summary

The mock circulation to test artificial hearts makes it possible for the left ventricle to pump against a diastolic pressure of 82 cm. of fluid and for the right ventricle to pump against a diastolic pressure of 27 cm. of fluid without constriction in the lines. Thus a stable system is obtained in which the pressures are to a large extent independent of variations in cardiac output. The fluid levels in the venous reservoirs indicate the venous pressures available to the right and left atria. The heights of the aorta and pulmonary artery can be varied, thereby altering the diastolic pressure to be overcome. Crossing over makes it possible to measure the flow rates on both sides with one flowmeter, once equilibrium is established.

**Manufactured by Fisher and Porter Co., Hatboro, Pennsylvania; Precision Bore Flowmeter Tube No. B-4-97-10/77.*

*†Manufactured under the guidance of Mr. Harry Norton by Thompson Ramo Wooldridge Inc., 23555 Euclid Avenue, Cleveland 17, Ohio.*

*‡Manufactured by Curtis Industries, Inc., 1130 East 222d Street, Cleveland 17, Ohio.*

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# SURVEY OF DIALYSES FOR ACUTE RENAL FAILURE AT CLEVELAND CLINIC HOSPITAL IN 1958

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THIS report presents the results of our most recent study of records concerning hemodialyses of acutely uremic patients. Our first study[1] was an analysis of the records of 38 patients dialyzed for acute renal failure in 1957; our current analysis concerns the records of the 27 patients dialyzed for acute renal failure in 1958. The correlation of the many variables has been facilitated by the McBee punch cards used in both studies.

## Methods

Dialysis removes retention products and corrects electrolyte abnormalities; ultrafiltration at the same time may remove excess fluid. The twin-coil disposable artificial kidneys were used, as previously described.[1-4] For small children, only one coil was utilized[5] and dialysis was continued for four hours; for adults, dialysis usually lasted six hours. The radial artery or greater saphenous vein was used to draw blood from the patient, any other vein to return it. Usually polyvinyl chloride cannulae[1] were used. For the saphenous vein, plastic tubing of (French) sizes 12, 14, or 16 with multiple holes was inserted to the level of the inferior vena cava. The catheter was left in place for continuous administration of 40 per cent invert sugar (Travert†) if needed.[1] If risk of hemorrhage existed, regional heparinization[6] was used, and the patient's clotting time was maintained at normal values. While 200 mg. of heparin in 1,000 ml. of 5 per cent dextrose in water was being administered by constant drip under pressure to the blood inflow tube of the artificial kidney, 150 mg. of protamine sulfate in 700 ml. of 5 per cent dextrose in water was simultaneously administered to the outflow tube.

The fluid intake of the acutely uremic patient was restricted to 600 ml. per 24 hours.[7] Electrolytes were administered only when they were demonstrably lost.[8] A forced high-calorie, low-protein regimen was instituted insofar as was practical.[9]

## Results and Comments

The analysis of the data concerning the 27 patients and 73 dialyses confirms the conclusions derived from the similar analysis[1] made for the preceding year. By summarizing the results of yearly analyses and perhaps also the experience of other centers now using an identical punch card system, statistically significant

*This study was supported by a grant to Doctor Kolff from the Life Insurance Medical Research Fund.*

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†*Obtained from Travenol Laboratories, Inc., Morton Grove, Illinois.*

results may be obtained. One card summarizes the data for one patient or may be used to summarize the total data for one year *(Fig. 1)*.

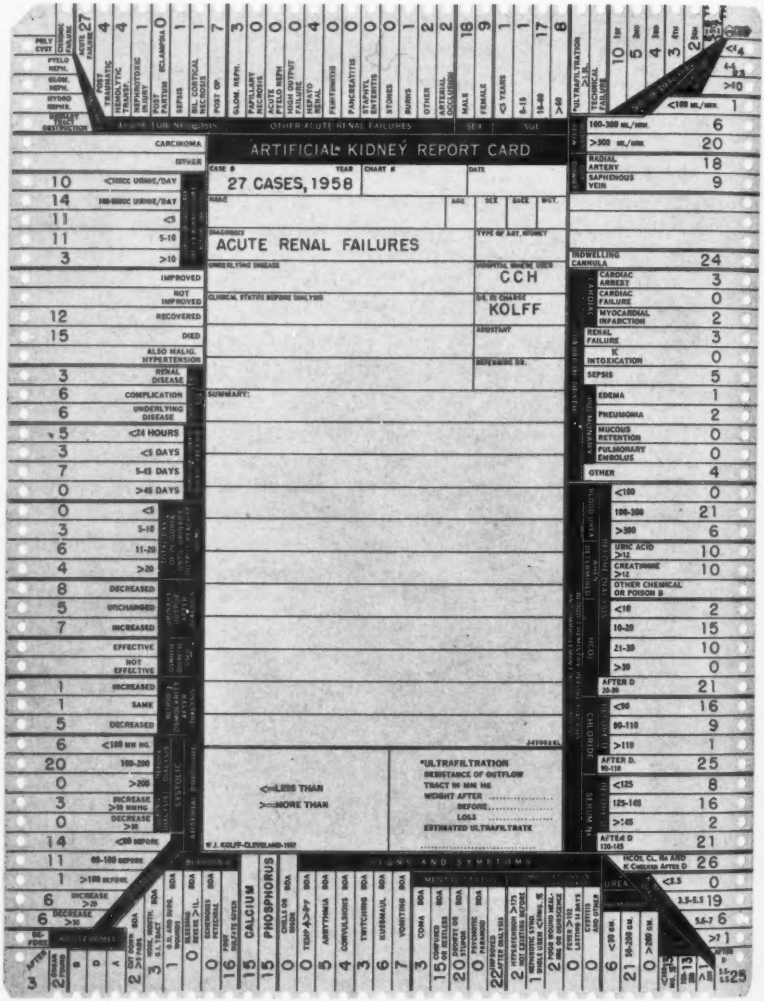


**Fig. 1.** The card shown in the photograph is used to summarize the data for 27 patients dialyzed in 1958. The data for each patient are filled in on his own card. The questions in the margin are answered with yes or no. For the positive answers the holes are cut open. A stack of cards is quickly analyzed with the help of an ice pick by "spearing" the particular item. The results of the summary can conveniently be entered on an extra card.

In 1958, 56 new patients were treated with a total of 142 dialyses. Twenty-seven patients (48 per cent) had acute renal failure and were treated with 73 dialyses; 12 (44 per cent) of those recovered; in 1957, 52 per cent of 38 patients recovered. Of the 15 patients (in 1958) who were dialyzed only once or twice, eight recovered. With more dialyses per patient, the percentage of mortality increased, but one patient recovered after five dialyses. Six of 18 men, and 6 of 9 women recovered. All six of the men more than 60 years of age died; only two women more than 60 years of age were dialyzed, one of whom survived.

*Diagnoses and causes of acute renal failure.* *Table 1* presents the list of common causes of acute renal failure as it is printed on our punch cards. The greatest number of patients had renal failure associated with surgical procedures. However, the

**Table 1.**—*Summary of data on causes of acute renal failure in and survival rate for 27 patients treated with dialysis at Cleveland Clinic Hospital in 1958*

| Diagnoses (order as on punch card) | Number of patients* | | |
|---|---|---|---|
| | Total | Survived | Died |
| Acute tubular necrosis | | | |
| Post-traumatic | 4 | 3 | 1 |
| Hemolytic transfusion | 4 | 4 | 0 |
| Nephrotoxic injury | 1 | 1 | 0 |
| Postpartum—eclampsia | 0 | 0 | 0 |
| Sepsis | 1 | 1 | 0 |
| Bilateral cortical necrosis | 1 | 0 | 1 |
| Postoperative | 7 | 2 | 5 |
| Other acute renal failures | | | |
| Glomerulonephritis | 3 | 2 | 1 |
| Papillary necrosis | 0 | 0 | 0 |
| Acute pyelonephritis | 0 | 0 | 0 |
| High output failure | 0 | 0 | 0 |
| Hepatorenal syndrome | 4 | 0 | 4 |
| Peritonitis | 0 | 0 | 0 |
| Pancreatitis | 0 | 0 | 0 |
| Staphylococcal enteritis | 0 | 0 | 0 |
| Stones | 0 | 0 | 0 |
| Burns | 1 | 0 | 1 |
| Other | 2 | 0 | 2 |
| Arterial occlusion | 2 | 0 | 2 |

*Three patients had two causes for acute renal failure.

high mortality, five of seven patients, was attributable to causes not immediately related to surgery. For example, three of the patients died of cardiac disease. One of the two patients in whom anuria developed after aortic grafting recovered.

Four patients with hemolytic transfusion reaction recovered and left the hospital. One reaction had occurred on the basis of sensitization to the Kell factor. This patient was readmitted because of severe serum hepatitis about six weeks later, and died. Three other patients had hepatorenal syndrome that was associated with hepatic necrosis, and all three died. It would be incorrect to conclude from the results in this small series that the artificial kidney has nothing to offer in cases of hepatorenal syndrome. Rather, the results confirm previous experience that when hepatic disease is progressive, the renal damage does not reverse either. However, a patient may be saved by dialysis from uremic death and may recover from the hepatorenal syndrome if the hepatic failure is reversible.

Two patients had renal arterial occlusion. In one patient occlusion occurred after an aortic graft; cholesterol-containing emboli of the small renal arteries led to focal cortical infarcts. The other patient had spontaneous renal arterial thrombosis related to severe arteriosclerosis and an aortic aneurysm. The diagnosis may be suspected on the basis of severe pain. Hypertension need not follow. Nothing short of arteriography can establish the diagnosis and the extent of the occlusion.

In *Table 1* two patients are listed under "Other." One had membranous glomerulopathy and acute tubular necrosis of unknown origin. The diagnosis can only be established by renal biopsy, and the treatment currently consists of large doses of corticosteroids. Sepsis at the end of a prolonged illness notwithstanding temporary improvement finally led to this patient's death. The other patient had a large myocardial infarction that resulted in shock, renal failure, and finally cardiac tamponade.

*Immediate causes of death.* If, in desperately ill patients in uremia, life is to be prolonged or perhaps saved, the currently prevailing causes of death should be recognized in the hope that they can be eliminated in the future. This is the purpose for the analysis in *Table 2*. There may be more than one contributory cause of death in a patient. Three patients died during dialysis, only one patient during the first dialysis; in 1957 there were no deaths during dialysis. These fatalities reflect the desperateness of the attempt to save life when the clinical outlook is almost hopeless. Constant supervision with a cardioscope during dialysis aims at earlier recognition of abnormalities in heart rate or in QRS pattern in the hope of avoiding sudden death. Some patients are indeed as much or more in need of a heart-lung machine as of an artificial kidney to prolong life. A combination of these services is being planned for the near future.

At the end of illness when all the data are available after a necropsy, it usually is possible to determine whether or not the patient was potentially curable when first examined. The records of the potentially recoverable patients can be traced

on our punch cards. It is in this category that future improvement of management and diagnosis should be rewarding. The necessity of profound diagnostic studies and alertness for new evidence is obvious; however, these patients should not be literally "studied to death," and often it is sound judgment to postpone diagnostic procedures in the hope that clinical improvement may be obtained first. Last year four patients died who could be classified as having had potentially recoverable disease. None of the patients who died this year could be so classified.

Of the four patients classified as having irrecoverable renal disease, one woman, aged 69 years had bilateral cortical necrosis and died 35 days after having virtually complete anuria. A 58-year-old man had an enlargement of the right kidney; biopsy revealed acute glomerulonephritis. Though the urinary output at one time attained 1,000 ml. per 24 hours, oliguria recurred and clinical evidence suggested progression to subacute glomerulonephritis. An aortogram revealed an obstructed left renal artery. At the present status of our knowledge, these diseases are irrecoverable.

Four patients had irrecoverable complications: overwhelming sepsis, septicemia, abscesses, and peritonitis. Three patients had irrecoverable underlying disease. One patient had a recognized myocardial infarction and unrecognized rupture of the left ventricle. Two patients were listed as having irrecoverable complications

**Table 2.**—*Immediate cause of death of 15 patients treated with dialysis for acute renal failure at Cleveland Clinic Hospital in 1958*

| Immediate cause of death (order as on punch card) | Number of patients* | | |
|---|---|---|---|
| | Total | Cause recognized before death | Cause not known until necropsy |
| Cardiac | 5 | 5 | 0 |
| Cardiac arrest | (3) | (3) | (0) |
| Cardiac failure | (0) | — | — |
| Myocardial infarction | (2) | (2) | (0) |
| Renal failure | 3 | 2 | 1 |
| Potassium intoxication | 0 | — | — |
| Sepsis | 5 | 3 | 2 |
| Pulmonary | 3 | 1 | 2 |
| Edema | (1) | (0) | (1) |
| Pneumonia | (2) | (1) | (1) |
| Mucus retention | (0) | — | — |
| Pulmonary embolus | (0) | — | — |
| Other | 4 | 4 | 0 |

*In one patient there may be two causes of death.

and irrecoverable underlying disease. One patient had necrosis of the liver as the underlying disease and multiple acute occlusions of the hepatic, splenic, and mesenteric arteries, and terminal aorta. The other patient primarily had post-necrotic cirrhosis with severe generalized ischemic necrosis of the liver and peritonitis as complications

*Survival time.* Five desperately ill patients died within 24 hours of the first dialysis. Four of these had to be dialyzed less than five days after the onset of renal injury, indicating the severity of their disease. Three patients lived 32, 34, and 36 days, respectively, after the first dialysis, although they later were proved to have irrecoverable disease. This is a testimony to the effectiveness of dialysis to maintain life even in the absence of renal function.*

*Degree and duration of oliguria.* Four of the six survivors with an initial daily output of less than 100 ml. required more than 20 days (24, 28, 30, 34 days respectively) for diuresis to occur. This confirms last year's observation that the more severe oliguria takes longer to recover from; however, the severity of oliguria does not predetermine the final outcome. Indeed, 6 of the 10 severely oliguric patients (but only 5 of the 14 mildly oliguric patients) recovered. This was the same ratio as the year before. One patient entered a diuretic phase after seven days of oliguria, but died in a late diuretic phase of complicating peritonitis. The occurrence of diuresis does not guarantee recovery.

*Chemical efficiency of dialysis.* Tabulations of chemical results show that although each dialysis led to improvement, the chemical pattern deteriorated again before the next dialysis. A continuous system of dialysis would be preferable though it is not practical. The next best solution is to dialyze repeatedly at short intervals; for example, every two or three days. We are doing this with gratifying clinical results. Five of the six patients with initial blood urea concentrations greater than 300 mg. per 100 ml. recovered. Serum uric acid and creatinine concentrations higher than 12 mg. per 100 ml. were followed by approximately 50 per cent survival, which is roughly identical to the survival percentage of the entire group.

Prognosis was not related to initial values of blood urea nor to electrolyte abnormality in this series; neither factor determines the patient's recovery. No difference in the extent of electrolyte derangement was found between those who survived and those who died. Dialysis corrects the initial chemical abnormalities so effectively that they play no role in the eventual occurrence of death, rather, the outcome is determined by the presence or absence of irrecoverable disease.

There were only two patients who had a carbon dioxide content reserve of less than 10 mEq. per liter. Both survived; one of them also had a blood urea concentration of 430 mg. per 100 ml. Both of those patients had normal serum sodium concentrations respectively of 145 and 143 mEq. per liter.

A blood urea concentration greater than 300 mg. per 100 ml. did not preclude

**One patient not described here because her renal disease was chronic, survived for seven days in the absence of effective renal function, thanks to dialysis.*

rapid recovery in one patient, but three of five patients with blood urea values higher than 300 mg. per 100 ml. needed more than 20 days to achieve diuresis. Again, as in the analysis of 1957,[1] there was no correlation between the severity of oliguria and the survival rate; between the degree of oliguria and the concentration of the blood urea; nor between the duration of oliguria prior to dialysis and the predialytic concentration of the blood urea.

In seven of the eight survivors with a blood urea concentration of more than 300 mg. per 100 ml., the serum creatinine content was more than 12 mg. and the serum uric acid more than 12 mg. per 100 ml. Only once was a uric acid value higher than 12 mg. associated with a blood urea of less than 100 mg. per 100 ml. These exceptions should be kept in mind. The blood urea concentration generally is an excellent though not infallible guide as to the severity of the renal failure.

## Summary

Twenty-seven patients in acute renal failure were treated at the Cleveland Clinic Hospital with 73 hemodialyses in 1958. The over-all recovery rate was 44 per cent as compared to 52 per cent in 1957. Eight patients were older than 60 years of age, of whom only one recovered. At the present status of our knowledge, 15 patients who died were considered hopeless because the renal disease (three patients), the complications (six patients), or the underlying disease (six patients) was irrecoverable.

The degree of oliguria again gave an indication for the duration of the renal failure. While the exact time of diuresis was unpredictable, more than 10 days was always required if the initial urinary volume after the insult (at the onset of anuria or oliguria) was less than 100 ml. per 24 hours. The duration of oliguria gave no clue as to the eventual outcome, since two patients who required more than 30 days for the onset of diuresis recovered. The efficiency of dialysis in correcting water and electrolyte disturbances and in removing nitrogenous products was again demonstrated. Not one patient in acute renal failure with potentially recoverable disease died.

*Data:* The original tables upon which this study is based and from which the conclusions are drawn are deposited at The Frank E. Bunts Educational Institute and are available for consultation upon request to the Director of Education of the Institute.

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# EFFECTS OF DESOXYCORTICOSTERONE AND SALT ON AN EXPERIMENTAL NEPHROTIC SYNDROME DUE TO LIGATION OF A RENAL VEIN

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A nephrotic syndrome has been elicited in a small proportion of rats that underwent subtotal ligation of the renal vein and contralateral nephrectomy.[1] A similar state has also been observed in rabbits, in which it was regularly intensified by an excess of salt given in the drinking water.[2,3] Our studies show that this effect of salt is likewise demonstrable in rats, and that by giving desoxycorticosterone acetate with salt to intensify further the effect, the pattern of renal injury is only complicated by a superimposed nephrosclerosis.

## Methods

The *effects of salt* were studied in three groups of rats. Group I, used as control, comprised 10 uninephrectomized animals; group II and group III comprised respectively 19 and 21 rats that underwent unilateral renal venous constriction and 12 days later contralateral nephrectomy. Drinking fluid consisted of 1 per cent sodium chloride solution, in groups I and II; in group III, tap water was first given starting at the time of renal venous constriction, followed by 1 per cent saline solution on the twenty-fifth day, and 1.25 per cent saline solution on the thirty-eighth day. The experiment was terminated on the fifty-second day.

The *effects of desoxycorticosterone acetate*† (hereinafter termed DCA) were studied in four groups of 10 animals each at the daily dose levels of 1 mg. of DCA (groups I and II) and of 0.2 mg. of DCA (groups III and IV); injections of DCA in aqueous suspension were given subcutaneously. Animals of groups I and III were uninephrectomized on the seventh day of treatment and were used as respective controls for those of groups II and IV which underwent unilateral renal venous constriction on the first day and contralateral nephrectomy seven days later. The experiments were terminated on the thirtieth day.

Sprague Dawley rats weighing from 90 to 110 gm. were used. Partial constriction of the renal vein was accomplished by tying a silk ligature around it and a stylet (diameter 0.55 mm.) that subsequently was withdrawn. Urinary flow, proteinuria, and arterial pressures were measured twice weekly. At the end of the experiment, total serum protein, blood urea nitrogen, and serum cholesterol values were determined, the animals were killed and the organs were removed for histologic studies.

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## Results

*Effects of salt.* Administration of 1 per cent sodium chloride solution in the control group I (uninephrectomy) caused diuresis in the average amount of 50 ml. daily (range 32 ml. to 83 ml.), while proteinuria remained about 30 mg. per day, which is normal in the rat.

In group II (renal venous constriction plus contralateral nephrectomy) administration of 1 per cent saline solution initially resulted in the same fluid and protein outputs as in group I. Then, about the seventh day postnephrectomy, while urinary flow remained unchanged, daily proteinuria increased in the range of 100 mg. to 500 mg. The mean serum cholesterol concentration was 121 mg. as compared 500 mg. The mean serum cholesterol concentration was 121 mg. as compared with 85 mg. per 100 ml. in the control animals, and blood urea nitrogen content was elevated to 29 mg. as compared with the control value of 20 mg. per 100 ml.; the total serum protein content was 6.8 gm. per 100 ml., which is normal.

In group III (renal venous constriction plus contralateral nephrectomy) tap water given during the first 25 days resulted in normal urinary flow and proteinuria *(Fig. 1).* Substitution with 1 per cent saline solution increased proteinuria to concentrations of about 150 mg. ; replacement with 1.25 per cent salt solution on the thirty-eighth day increased proteinuria to concentrations in the range of 500 mg. to 900 mg., and diuresis to 100 ml. daily. Beginning at about the fifth day of administration of hypertonic saline solution (1.25 per cent), body weights began to fluctuate widely as a result of phasic fluid retention and excretion; blood pressures at that time were greater than 200 mm. of Hg *(Fig. 1).* In two of four survivors, the total serum protein content was less than 6 gm. per 100 ml. ; serum cholesterol content was more than 200 mg. and blood urea nitrogen was more than 50 mg. per 100 ml.

In groups II and III operative mortality due to excess renal venous constriction and uremia was about 50 per cent, with development of a nephrotic state in about 25 per cent of the survivors; this represents an incidence of about 10 per cent in the salt-treated groups. The renal lesions in these animals resembled those described previously.[1] With 1 per cent sodium chloride they were limited to glomerular basement membranes; these were irregularly frayed and focally impregnated with material in droplet or diffuse form giving a positive reaction with the periodic acid-fuchsin stain. With 1.25 per cent sodium chloride, lesions involved both glomeruli and tubules. Glomeruli showed the above membranous changes, accompanied by simplification of tufts, focal proliferative changes and exudate in subcapsular spaces. Tubular basement membranes were thickened and the lumens contained casts.

*Effects of desoxycorticosterone and salt.* In the control group I (uninephrectomy plus 1 mg. of DCA), proteinuria remained normal until the tenth day when it increased and reached a maximum of 300 mg. between the fifteenth and twentieth days. In the experimental group II (renal-vein ligation plus uninephrectomy plus

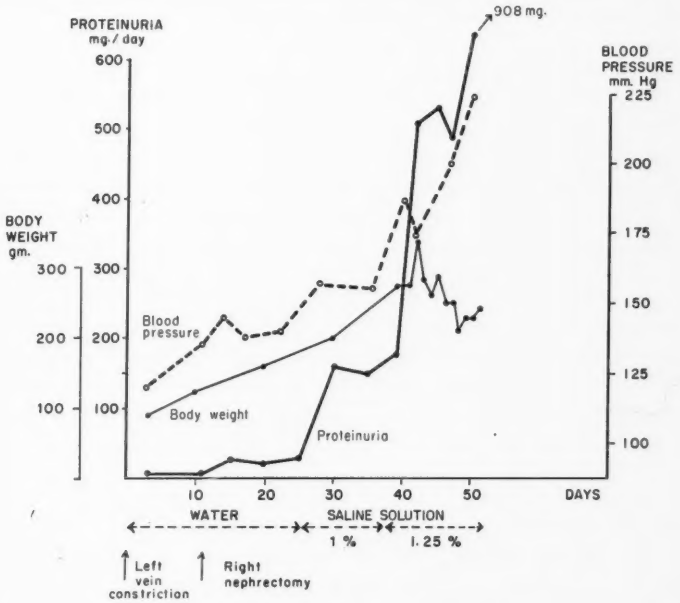


Fig. 1. Graph showing the effects of drinking water of 1 per cent and of 1.25 per cent saline solution in a rat with renal venous constriction and contralateral nephrectomy.

1 mg. of DCA) proteinuria increased rapidly about the tenth day to reach a maximum of about 600 mg. During the period of intense proteinuria, these rats showed crises of phasic fluid retention and excretion: one animal's weight increased from 182 gm. to 219 gm. during 24 hours, and decreased to 152 gm. during the next 24 hours. The experiment was terminated on the thirtieth day. Mean blood pressures, serum cholesterol values and protein concentrations were alike in both groups. At necropsy, the kidneys were large and pale with irregular surfaces. Splanchnic arteritis was present in two of the the five survivors in group II. In both groups kidneys showed histologic nephrosclerotic changes that were more severe in group II. In the latter group these were superimposed upon and masked any possible membranous changes so that differences between the groups were barely noticeable.

The effects of DCA at the dose level of 0.2 mg. (groups III and IV) were qualitatively similar to those just described in groups I and II.

## Discussion

Excess sodium chloride given in drinking water intensified the nephrosis induced by renal venous constriction in rats, as it did in rabbits.[2,3] The intensifi-

cation is associated with augmented proteinuria and phasic fluid retention, and is greater with 1.25 than with 1 per cent saline solution used as drinking fluid. The situation is reminiscent of that evoked by prolonged administration of salt,[4] and the syndrome elicited by the administration of renin.[5,6] Difficulty in producing it in rats is apparent from our data. Other investigators[7] have attributed their failure to the small size of the renal pedicle.

The experiments in which DCA was given to increase salt retention do not show noteworthy further intensification of the nephrotic process. This is because they were complicated by hypertension and its associated lesions, so that the pattern of renal injury was too complex for comparative analysis. This rapidly hypertensive effect even of small doses of DCA, again demonstrates the enhanced pressor effects of this agent when given in the presence of a sufficient, but not of itself hypertensive degree of renal injury. Such effects have been described as occurring in rats treated with antikidney serum,[8] or subjected to perinephritis[9] or to figure-of-eight renal ligation.[10]

## Summary

Administration of salt (1 per cent sodium chloride solution as drinking fluid) to rats with partial renal venous constriction produced a nephrotic state, including glomerular basement membrane changes; substitution with hypertonic (1.25 per cent) saline solution, intensified the syndrome. However, the procedure remains technically tedious and results in an incidence of about 10 per cent of nephrotic animals. Any further intensification of the nephrotic syndrome by desoxycorticosterone acetate was obscured by the nephrosclerotic effect of the steroid.

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## ANNOUNCEMENTS

### Physician-in-Chief Pro Tempore

Stewart G. Wolf, M.D., Professor of Medicine, University of Oklahoma School of Medicine, Oklahoma City, Oklahoma; and Chairman of the Professional Education Committee of American Heart Association, will be the ninth annual Physician-in-Chief Pro Tempore on December 17, 18, and 19, 1959. During his tenure, Doctor Wolf will direct the teaching program of the Fellows in Medicine, including conferences, lectures, and daily clinics. Members of the medical profession are cordially invited to attend.

## Surgeon-in-Chief Pro Tempore

Owen H. Wangensteen, M.D., Professor of Surgery and Chairman of the Department, University of Minnesota Medical School, Minneapolis, Minnesota, will be the seventh annual Surgeon-in-Chief Pro Tempore on January 7, 8, and 9, 1960. During his tenure, Doctor Wangensteen will direct the teaching program of the Fellows in Surgery, including conferences, lectures, and daily clinics. Members of the medical profession are cordially invited to attend.

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